FOOD AND DRUG ADMINISTRATION (FDA)

CENTER FOR DRUG EVALUATION AND RESEARCH (CDER)

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

Docket No. FDA-2017-N-2903

Tuesday, July 11, 2017

Sheraton Silver Spring Hotel

8777 Georgia Avenue

Silver Spring, Maryland 20910

Reported by: Michael Farkas

Capital Reporting Company

PARTICIPANTS

Scott Gottlieb, MD, Commissioner, FDA

Doug C. Throckmorton, MD, Office of the Center Director, CDER, FDA

Judy A. Staffa, PhD, Office of Surveillance and Epidemiology, CDER, FDA

Mark Levenson, PhD, Office of Biostatistics, CDER, FDA

Kunthel By, PhD, Office of Biostatistics, CDER, FDA

Cynthia Kornegay, PhD, Office of Surveillance and Epidemiology, CDER, FDA

Hana Lee, PhD, Office of Biostatistics, CDER, FDA

Jana McAninch, MD, Office of Surveillance and Epidemiology, CDER, FDA

Tamra Meyer, PhD, Office of Surveillance and Epidemiology, CDER, FDA

Diqiong Xie, PhD, Office of Biostatistics, CDER, FDA

PANELISTS

Jonaki Bose, NSDUH

Edward W. Boyer, MD, Brigham and Women's Hospital

John T. Brooks, MD, CDC

Daniel Budnitz, MD, CDC

Theresa Cassidy, MPH, Inflexxion, Inc.

Daniel Ciccarone, MD, UCSF
Wilson M. Compton, MD, NIH, HHS
Frederick Conrad, PhD, University of Michigan
Elizabeth H. Crane, PhD, SAMHSA
Nabarun Dasgupta, PhD, UNC-Chapel Hill
Carol DeFrances, PhD, NCHS, CDC
Louisa Degenhardt, PhD, University of New South Wales
Barry Graubard, PhD, NCI, NIH, HHS
Jody L. Green, PhD, RMPDC
Christopher M. Jones, Capt., HHS
Erin E. Krebs, MD, Minneapolis VA Health Care System
Peter W. Kreiner, MD, Brandeis University
Vincent Lo Re, MD, University of Pennsylvania
F. Leland McClure, PhD, Quest Diagnostics
Richard Miech, PhD, University of Michigan
Scott P. Novak, PhD, Battelle Memorial Institute
Jennifer D. Parker, PhD, NCHS
Elizabeth J. Scharman, PharmD, WVU
Sidney H. Schnoll, MD, Pinney Associates
Abigail Shoben, PhD, OSU
George Jay Unick, PhD, University of Maryland
Almut Winterstein, PhD, University of Florida

TABLE OF CONTENTS

P R O C E E D I N G S

DR. LEVENSON: Good morning. Just to review, my name is Mark Levenson. I'm the division director of the Biometrics Division in CDER. I'm going to talk about some housekeeping now for a few minutes, as people settle in, and then we're going to have a few words by the deputy center director, Doug Throckmorton.

Okay. So, thank you for your participation. I think the first day there were some great ideas. I think we already have some ideas that we can go back and think about implementing, and there will actually be more discussion at the end of the day what the next steps are. So, I think the first day was great and I look forward to this second day. And I actually feel people were dying to talk about a lot of topics that were second-day topics anyway, so I think this will be a very fruitful day.

So, before we begin, some housekeeping details. Please silence your cell phones and other devices. Please check in at the tables outside in the lobby, if you haven't done so. Agendas and discussion questions are available at the registration tables. I

think the panel members have them at their tables. All the meeting documents, including the slides, have been posted on the FDA webpage for this meeting. Transcripts of the meeting will also be posted approximately six to eight weeks after the meeting. The restrooms are still down the hall. When it comes time for the public sessions, we'll review the procedures of that. I won't go over that now.

But now I'd like to introduce Dr. Doug Throckmorton. Dr. Throckmorton is the deputy director for regulatory programs at CDER at FDA. Dr. Throckmorton has many duties as deputy center director, but he is a leader in promoting the safety of prescription opioids. And as you can see from day one, he is keenly interested in this topic. So, Doug, thank you for providing some opening remarks today.

DR. THROCKMORTON: Thanks, Mark, very much, and I appreciate everyone that's come, everyone that's on the web, and everyone who was able to participate yesterday. I agree with what Mark said. We've heard some terrific discussion. I'm looking forward to this afternoon's discussions and this morning's, also, Mark,

I confess. So, I'm eager to get to those as quickly as we can.

You heard yesterday from the commissioner about the broader context of our approach to the opioids crisis, clearly reflecting the importance that this plays for the Agency's mission, that the things that we're doing day-to-day, it's at the top of our agenda. I talk with him almost daily about the things that he has in mind for us to do. He is committed to making a difference in this particular public health crisis, along with many others. It is one of our highest priorities. What I'd like to do just briefly is place the abuse-deterrent formulations in that broader context to help us remember the importance that the Agency places in this particular part of that larger response.

AD opioids, we continue to believe are one aspect, one important tool to take down and use under appropriate circumstances to try to address the opioids crisis. There is a lot we don't know about them, a lot that you guys are helping us to learn about them, but we continue to believe that they are one tool that has

enormous potential. Given that, we have committed substantial resources to supporting their development, assessment and appropriate regulation, and we can talk about the policies that we put in place, the regulations that we've thought about undertaking, the guidances that we put into place in the last couple of years to try to steer the development of abuse-deterrent formulations. The point is that the Agency believes that they're important. The Agency has committed resources to them to try to make them appropriately used.

We have a goal, and let me just read it, because it's important. Our goal is to incentivize the development of opioid medications with progressively better abuse-deterrent properties and support their widespread use. That's a goal that we have articulated now for the last couple of years. It continues to be one of the goals, the second being a goal related to generics availability to guide our actions in the AD formulation space.

You guys are helping us with the central issue as regards to making progress in the abuse-deterrent

opioids. We need to know whether they work in the real world. Judy Staffa said that yesterday. That is exactly the question we need answered. Now, Erin and others asked what that exactly meant. We can get back to that conversation if you need to, but fundamentally that is a question that needs answered for us to take the next steps, to take the next kinds of steps that we want to take to understand and support the best possible uses of AD opioids.

We know it's not easy. We know you guys spent the day yesterday talking about how hard it is, hard to decide exactly what it means to say that they work in the real world; hard to find the data that you'd like to answer that question; hard to look to the data systems that are available to prove the data to get the answers that we want to have.

The challenges were articulated well by all of you. Ed Boyer's comment about the dextromethorphan reporting I thought was really telling as regards to the limitations of the kinds of data that we have to have here. Several of you recommended alternative approaches, looking at other indirect measures of abuse

and misuse of opioids as possible ways of assessing the impact of abuse-deterrent formulations. Technological effects were suggested, for instance. Deterring insufflation or extraction in a clinical study of some kind, or focusing on AD formulations with properties that are directed to dose and then making inferences from those kinds of things. I think that has obvious potential. We need to make certain that the new products with other technologies that don't focus on crush and extraction resistance could be assessed also using those kinds of studies.

People suggested street price, and it has an on-face attractiveness, doesn't it, as you think about street price. If someone is willing to pay more for a product, it may be that it's more attractive to them for other purposes. Several speakers yesterday mentioned drug diversion data, ARCOS or other systems, as a possible clue to understand the effectiveness of AD formulations.

And then, finally, some people suggested other sort of biomarker kinds of approaches that could be used. All of them have potential; all of them would

need to be validated. We would have to understand the link between those indirect measures and that clinical outcome that I dearly want, to know whether abuse-deterrent formulations deter abuse in the real world.

So, today you are going to continue to give us important suggestions, and I'm really looking forward to that. As you do that, I just want us to all remember that as we think about the challenges of the systems, the challenges of the data, the challenges of making progress here, remember that we are in the midst of a public health crisis. We have 40,000 people -- choose your number -- dying of overdose each year, and we need to make certain that our response is both appropriate and scientific and timely and impactful. So, we have to balance the need for the best possible data with sufficient data for us to make the right regulatory decisions for the best possible public health outcome.

I hope as we talk today you continue to keep the ideas coming. I really appreciated the end of the day yesterday with the detailed suggestions you made as far as methodologic approaches that we should be

taking, additional analyses that we may not have thought about. I understood about 10% of them, but fortunately everybody to the right of me at the table understood them and I know was listening very carefully. Those are exactly the kinds of things we brought you guys together to give us, to point out thing we haven't thought to do, because this group is working tremendously hard. Any new suggestions absolutely welcome.

So, for today we're going to continue our discussion. I'm looking forward to listening as much as I possibly can. As I said before, in the midst of this public health crisis, FDA believes that abuse-deterrent formulations have a place, a place that we need your help to define. This is more than just ADFs, but for today, for this meeting, we really need to ask for your help in clarifying their value and clarifying how best we can understand their use in addressing the opioids crisis. Thanks very much.

DR. LEVENSON: Thank you, Doug, for those words. I think they will set the day off right. So, thank you very much. So, like yesterday, I'm going to

start today with an opening, like Judy did yesterday, start today with an opening presentation that is going to provide a roadmap for day two. So, first I'm going to review some of the overall objectives of this workshop and then provide some examples of day two datasets, and then describe the outline for the day.

So, just to review, day one was focused on improving the use of existing data sources used in ADF evaluation, but day two is focused on the use and development of new sources and capabilities for ADF evaluation.

So, again, just to review what the objectives of this is, according to the 2015 Guidance on Abuse-Deterrent Formulations, the objective we're trying to achieve here is to determine whether the marketing of a product with abuse-deterrent properties results in meaningful reductions in abuse, misuse and related adverse clinical outcomes, including addiction, overdose and death in the post-approval setting.

In addition to that, we'd like to determine whether products discourage riskier forms of abuse and misuse. For example, whether they discourage IV use as

opposed to oral use. So, that's also an objective that would be worthwhile to achieve.

So, the guidance talks about populations that we're interested in, and, again, I quote from the guidance here. At least one study should include a high-risk population such as the population of known drug abusers, but formal studies should not be limited to only high-risk populations. So, some examples of populations might be known drug abusers; on the other end of the spectrum might be patients with a new prescription. And somewhere in the middle might be somewhat this vague notion of patients on the verge of abuse, patients who have been using opioids and may at a certain stage be prone to abuse, whether the ADF will have an effect on moving to abuse outcomes.

We have certain requirements to achieve this. It's important that we have product-specific information, including brand and formulation. FDA makes labeling for particular products, so we need specifics on products and formulations. We need -- whatever system we use we need information on the routes of abuse, because as was mentioned several times

yesterday, products do not necessarily deter all routes -- or not intended to deter all routes of abuse and are designed for specific routes of abuse. So, we have to know how the product is being abused.

We need the ability of any sort of system to rapidly be modified in response to changes in the prescription drug market. New drugs will come on the market, there will be changes in the opioid market, and whatever system we employ has to be adaptable as the market changes. As was mentioned yesterday, we need rigorous and valid outcome ascertainment. We have to believe the outcomes we're measuring.

And this was also discussed yesterday in terms of the causal session. We need comparability over products and stability over time in the system in order to probably make causal statements.

We need well-defined populations. This could be done through probability sample or otherwise, but we have to know who we're actually trying -- who we're studying and what we're making inference on. And we need the ability to measure different populations. As the guidance said, we're interested in different

populations at risk, but we also may be interested in different regions and demographic subgroups.

As you heard yesterday, some drugs have very small market share, so whatever system we use has to be able to handle drugs with a small market share. To accomplish this, we may need multiple data sources and studies. It's not probably reasonable to assume that one data source and one type of study can accomplish all this.

So, just for concreteness, I'm going to go through several examples of the type of data we're going to discuss today. So, we'll have sessions on probability samples, and we're going to have a session on what's called following patients over time, and the primary example of that would be a cohort study. And I'm also going to discuss a study that's not about opioids but has similar objectives to what we're trying to achieve today, and is sort of a combination of a probability and a cohort sample, just to show that it may be not be one or the other that provides a solution. If there are ways of using aspects of both designs, that may be helpful.

So, I'm not an expert on any of these studies, and there are panel members that are experts on these studies, at least the first two. But I'm just providing them as concrete examples so we're all sort of talking the same language as we start the day.

So, first I'm going to discuss the NSDUH survey as an example of a probability survey. So, NSDUH is a multi-stage area probability design. So, in the first stage strata are formed based on states and regions, so that covers the whole US. From there, the four stages of probability sampling occur. In the first stage, census tracks are chosen by random, and the second stage, census block groups are chosen by random, and then census block clusters, and finally households within those clusters are chosen at random. An algorithm is used to select members of the household for the detailed survey.

So, this is an example of a multi-stage area probability design. So, youths age 12 to 17, and young adults are over-sampled in this. The prescription drug use is focused on a 12-month period, and there are questions on misuse. And the drugs are identified

using electronic images of pills.

Okay. So, as an example of a cohort study, I'm going to use this FDA postmarket requirement 3033.2. For those of you who are not familiar with a postmarket requirement, FDA has the authority to require from the drug manufacturers to conduct studies under certain circumstances, and those are called postmarketing requirements. And several years ago FDA required the manufacturers of all extended release, long-acting opioids to conduct a series of postmarket requirements, and this is just one of them. Actually, it's one and some supporting studies.

So, this was a study where we asked industry to conduct an observational study using patient health records, insurance claims and death records. So, this is basically a study in administrative data. So, a group of patients initiating opioids, and that's well defined with well-defined inclusion/exclusion criteria, are followed over time for some predefined outcomes. And those outcomes were developed in two companion studies. So, two companion studies developed and validated algorithms using coded medical terminology

for overdose, death, abuse and misuse. So, we're going to talk a little bit more about this in the cohort session later in the day, but just for a little concreteness, this is one example of a study that is being conducted.

So, now some general comments on probability samples and cohort designs. First probability samples. So, probability samples, subjects are randomly selected from some well-defined population. There may be longitudinal information collected. You can follow the same subjects over time or there may not be; it may be more cross-sectional in nature. And because of the way the population is chosen based on probability, rigorous inference to the population is possible. And from this inference you can calculate quantities such as incidents based on these population quantities. So, you can calculate the incidents of subjects with a given exposure -- incidents of an event with subjects with a given exposure based on these population estimates.

Now, a cohort design by what we mean today, and it might mean different things in different

settings, but this is a design where it's based on some subjects satisfying some well-defined inclusion/exclusion criteria. The subjects have longitudinal information on exposure, risk factors, and are at risk for the outcome. And incidents and relative risks are based on aggregating the subject level information. So, again, we can calculate incidents in this case by sort of aggregating the relevant subjects.

So, a few kind of thoughts on comparing these two designs, the cohort and the probability sample. The good news is they both provide a direct denominator. This is in contrast to the datasets that were the focus of day one, which was numerator-only datasets, and the denominator came from some other source of data that was the discussion of the second session of the day. So, both of these designs have big advantages. They provide a direct denominator.

The inferred population differs between the two studies, so strictly the cohort, the inferred population is just a cohort, but you may use judgment or some standardization to apply to some larger group.

The inferred population for the probability sample is the population from which it's drawn. As I said, they both allow valid estimates of incidents, and because you have patient -- subject level information, you can explore relationships. In addition to exploring relationships, you could probably employ additional methodologies, like propensity scores that we discussed yesterday. So, because we have that subject level information, both for people with and without events for different exposures, there is a lot of methods that are available for these sorts of data.

The two studies share similar challenges, although they may be expressed differently. The challenge in the cohort is identifying the appropriate cohort and getting the information you want from them. It's actually kind of similar for the probability sample is the sampling or enriching for certain populations and then obtaining information for them. So, there are still -- there are challenges, as I'm sure you're well aware, and those challenges will be important to discuss today as we try to make a system that's actually usable for us.

I'm just going to spend a moment on this slide, which is a little complicated, that actually gives us a little concern about cohorts and actually probability samples as well. This was a study by Dr. Lisa LaVange, our office director in Biostatics in CDER. This was before she came to CDER. It compares a probability estimate with a simulated cohort study. Now, the simulated is actually -- you'll see in a moment, it's not too simulated. So, this comes from this survey, the Medical Expenditure Panel Survey. It's a probability survey, and from that survey which was a real survey, a simulated cohort was formed for this analysis. The simulated cohort consists of patients who had one or two clinic visits in the last year. So, some sort of patients that had some sort of clinical encounter, which might be a reasonable way to form a cohort.

So, this bar chart compares the outcome, average number of workdays missed due to illness or injury for the sample based approach, which is the white bar, for this cohort which is this slightly shaded bar. And the dark bar is standardizing the

cohort to the population. And it doesn't take a lot of thought to understand why this cohort is biased, but it is sort of a reasonable cohort, and you can see that the cohort or even standardizing it to the population doesn't quite give you what the population estimate would. Now, this -- I'm not trying to say that probability samples are always going to be better than cohorts, but you do have to worry about the representation of both of them.

So, now I'm going to say, as my last example, a few words on this Hispanic Community Health Study. This is an example that uses elements of cohort studies and elements of probability samples, and I think in a very effective way. It's not a study on opioids, but it actually has objectives that are not too different from the objectives we're looking at today. So, the objectives, just for concreteness, was to estimate prevalence of baseline risk factors and explore relationships between risk factors and health outcomes.

It was a probability sample embedded in a multi-site cohort study and I'm going to say more about that. The size was about 16,000, and it had

longitudinal aspects, so let me talk about the design, which is mainly what I'm interested in here.

So, the design consisted -- it started with four cities in the US, and these cities were not chosen randomly; they were chosen because they were enriched with Hispanics and they provide a certain breadth of what the investigators felt of Hispanic communities in the US. So, the first stage was this nonramdom selection of four communities, which is actually four cities in this case. From those communities there was another nonrandom stage that census tracks. They were in close proximity to clinics and also provide some breadth as well, and that breadth was a little bit quantitative, but I won't go into now. But this was, again, based on judgment, census tracks were chosen. So, in some sense the census tracks are cohorts now.

But from these census tracks there were two stages of random sampling. First, census blocks were chosen and then households were chosen in that. So, you do get a rigorous representation within these sorts of judgment-selected cohorts. So, I'm bringing this study up as an example that it doesn't necessarily have

to be either/or, that you can use elements of both cohorts and probability sampling.

So, those are my examples. I'm going to just conclude with our sort of outline and what we're trying to accomplish today. So, in day two, again, we have four sessions. The first session is on national surveys, and this is both on the use of existing national surveys for our present purposes, as well as opportunities for new surveys or supplementing existing surveys, and that will be our first session of the day.

The second session has this kind of lengthy title: Designs that Assess Exposure and Outcome in the Same Individuals over Time. The prime example of that is a cohort study, but we don't want to limit the discussion to just cohort studies, and that idea will be further expanded in that session.

The seventh session, the third of the day, is on leveraging other data, and linking and benchmarking. Some of these ideas came up in the first day. This is both linkage to get more information on the same patient, or benchmarking, where we're using some sort of standardization to apply to some known population.

So, I think that will be a very fruitful session.

And, finally, in last session we'll sort of sum things up, as we did yesterday, try to probe a few of the ideas that came up throughout the day. But in addition to that, we really want to see what the next steps are that we can do at FDA. We heard a lot of good ideas today. I actually expect today will be at least as fruitful, but we want to leave this with where FDA can go from that. So, Judy and I will try to probe this and feel what sort of concrete steps we can do to both -- as Doug said, you get something working in the near term and then also maybe get something perhaps more -- that has greater features in the long run. So, that will be our final session of the day.

So, here is some of the discussion and feedback we seek today. So, we're interested in the utility, strength and limitations of the existing national surveys; approaches and feasibilities to modifying existing national surveys; the development of new surveys, including Internet panel surveys and other designs; novel study designs, including longitudinal cohort studies and leveraging and linking multiple data

sources. And we're also interested in maybe -- maybe this didn't come out as much, but we have found this useful in previous studies -- smaller or local regional studies or other types of information. So, if you have some great idea that doesn't fit into any of the sessions, feel free to try to squeeze it in.

So, that's the roadmap for day two and that's some of the discussion we're seeking. So, we'll start our first session today, which is on the national surveys, and it's going to be moderated by Dr. McAninch and Dr. Xie, and Dr. McAninch will have the opening presentation. Thank you.

SESSION 5: BUILDING ON ESTABLISHED NATIONAL SURVEYS

DR. MCANINCH: Good morning. Again, I'm Jana McAninch, and I'll be moderating -- speaking and moderating the session with Dr. Xie on opportunities using national surveys and other types of surveys to evaluate ADFs in postmarketing setting.

So, in this session we'll be discussing the potential for national surveys to help us understand the impact of abuse-deterrent opioids. And just to introduce the session, I'll briefly discuss why we're

particularly interested in this type of data, describe several of the established national surveys, and discuss whether there might be opportunities to build on these to evaluate ADFs. And then I'll describe some of the, I guess, more emerging survey methodologies in this space, primarily Internet-based surveys. And then, finally, what would be some key elements to a population survey that is designed to evaluate ADFs. And, of course, we'll go to the discussion questions.

So, why are we devoting a whole session to the topic of national surveys? Well, first, some of the outcomes that we are interested in are really behaviors with a particular intent. So, as opposed to medical diagnoses or reportable adverse events, and therefore they may be best captured or perhaps only able to capture using self-reported data.

And, second, much of the data that we currently rely on is, in essence, based on passive surveillance, so where we're relying on people to call into poison centers or to present for substance use disorder treatment. And we're interested in active surveillance systems where the selection to the sample

is not by definition dependent on the outcome that we're measuring. So, the major established national health-related surveys also have the advantage of using probability sampling, as Mark just described.

We know that drug abuse patterns vary widely by geographic region, by urbanicity, and we can't assume that the prevalence and patterns of abuse that are measured in a convenience sample reflect the nation as a whole, which is typically what we're interested in as a federal regulatory agency. And the use of probability sampling also allows us to make inferences to a defined underlying population and facilitates valid comparisons between products and over time.

So, I know several of the existing national surveys have been discussed briefly. I'll go into just a little bit more detail with an eye to what types of data would be particularly valuable for evaluating the impact of ADFs. And we have a number of panelists today who have expertise both on conducting and analyzing data from these types of surveys. So, we hope to have some really fruitful discussions.

So, we've heard some about the National Survey

on Drug Use and Health, or NSDUH, which is an ongoing nationally representative, face-to-face population survey on the civilian, noninstitutionalized US population, age 12 years and older, and this is sponsored by SAMHSA. And based on interviews of approximately 70,000 participants each year, NSDUH is able to provide national estimates on self-reported drug-taking behaviors, including misuse of prescription pain relievers.

And NSDUH underwent a major survey redesign, which was implemented in 2015, and this did result in a trend break. But it now provides more detailed information on past year use and misuse of specific opioid molecules as well as more information on the reasons for that misuse. But with a couple of exceptions, NSDUH still collects fairly limited information on recent misuse of specific opioid products and on routes of abuse.

So, I know that this is a pretty small print, but it's just an example of a table from SAMHSA's published results from the 2015 NSDUH survey showing estimates for past year use and misuse of opioids. So,

there are a couple of specific products, as you see, but the rest are at the molecule level. And in the left-hand column you have the estimated percentage of people who have used a particular opioid in the past year, so that's either as directed or otherwise. And in the next column you have the estimated percentage of people who have misused the opioid, which is broadly defined as using it in any way not directed by a doctor. And then in the last box is the proportion of users of a particular opioid who reported misusing it in the past year. And we find this to be a pretty interesting metric, perhaps giving some insight into the likelihood that a particular opioid will be misused by an individual who is exposed to that opioid. So, we would be interested in the panel's thoughts about this type of metric or how it could perhaps be refined to get at abuse behaviors even more specifically, including route of abuse.

So, NSDUH has been used to study trends in nonmedical use of OxyContin, and Capt. Jones was one of the authors on one of those studies. But we're interested in a discussion about how NSDUH could be

used to help evaluate other ADFs. And particularly thoughts on the potential for new or revised questions or modules, keeping in mind sample size and the ability to get sufficiently precise estimates for products with low market share or a low prevalence of nonmedical use. And then, of course, this is already a fairly lengthy interview, and we wouldn't want the burden of additional questions to adversely affect response or completion rates.

I also just wanted to briefly mention some other national public health surveys, just to get people thinking about what other methods might possibly help us in evaluating ADFs. So, first in Monitoring the Future survey, which is, again, a longstanding NIDA-sponsored school-based national survey that is focused on adolescents. And this survey asks about use of a wide variety of substances, but in general, again, it's not possible to distinguish specific products by brand or formulation. And Monitoring the Future does also have a longitudinal component, where a subset of students complete follow-up surveys after high school.

The National Health and Nutritional

Examination Survey, or NHANES, includes not only interviews, but also physical exams and laboratory testing, and it has a longitudinal follow-up component as well.

The National Health Interview Survey is a large national health-related household survey that uses methods that are fairly similar to NSDUH.

The Behavioral Risk Factor Surveillance System is a health-related telephone survey of more than 400,000 adults each year, and it uses a modular questionnaire with a core component and then optional modules and questions that can be added by individual states.

The Youth Risk Behavior Surveillance System is another school-based survey that monitors various health risk behaviors including alcohol and drug use, and these data can be analyzed at the national, state or even the district levels for local policy-making.

And then finally the Pregnancy Risk Assessment Monitoring System, or PRAMS survey, which surveys women who have had a recent live birth, sampling from state birth certificate files. And they also over-sample

women from some high-risk groups and conduct follow-up, longitudinal follow-up surveys as well.

So, there will clearly be some big challenges using these types of national surveys to collect data at the level of detail that we need to evaluate ADFs. These are already fairly lengthy surveys. There are typically a variety of stakeholders and topics that need to be covered, and it's not easy to change these questionnaires quickly to include new products as they enter the market. And, also, the household and school-based surveys may not be capturing people that are at highest risk for the outcomes that we're interested in. So, we might miss important trends that are occurring in these higher risk subgroups, and there would likely be low precision for the less commonly used products and routes of abuse. And these large surveys, of course, require quite a bit of time to clean and prepare the data before it becomes available to users.

So, I also just wanted to touch on some emerging survey methodologies, specifically Internet-based surveys, which we heard a little bit about yesterday, but we'd like to have some more discussion

about these today.

So, this is something we've recently been seeing more of in the prescription drug abuse research space and of these opt-in Internet survey panels where a survey administration company recruits individuals to subscribe to an online panel, who can then participate in various surveys. They typically use some type of sample matching or weighting techniques to try to obtain a sample of demographic distribution that is similar to your target population. And these surveys can be tailored to examine specific products or look into specific research questions.

So, both of the major proprietary drug abuse surveillance programs, Inflexxion and RADARS, have conducted these types of Internet-based surveys using opt-in panels, and we have panelists today from both of these groups. For example, in 2015, Theresa Cassidy and the group at Inflexxion published a descriptive study on nonmedical use of prescription stimulants using the survey research company YouGov. And then Jody Green and the group at RADARS have recently launched a new survey program called NMURx in the

United States, which uses established online survey panels to examine nonmedical use of prescription drugs more broadly. And they use multiple methods for recruiting participants. And the survey includes estimates for lifetime, past year and past 90, 30 and 7-day nonmedical use of specific products. And it also includes information on route and reasons for nonmedical use.

So, another interesting approach that we encountered recently is the recruitment of survey participants from visitors to online drug discussion forums, such as Blulight.org, which essentially enriches the sample with people who have drug abuse experience. There were several recent Internet surveys conducted by Inflexxion using this type of recruiting to evaluate, to study nonmedical use of hydrocodone.

So, I think that the Internet-based recruitment raises some interesting questions about sampling, and we have some experts here who can talk about that more. But, for example, what is the underlying population for these opt-in panels exactly? And what about for studies that recruit from drug-abuse

discussion forums? And what kind of selection forces might be operating and might change over time given the evolution of Internet and social media use. And can we make valid inferences to some defined underlying population?

And, finally, I think that the relative ease of modifying these types of Internet-based questionnaires is a real potential advantage, but we still need rigorous questionnaire development and validation to get high quality data that we're looking for.

So, before we get to the discussion questions, I just wanted to summarize what we see, again, as some of the key elements of an ideal national survey for use in evaluating abuse-deterrent opioids. So, again, of course, we need data on specific products, and route of abuse is very important. We need to be able to rapidly modify the survey in response to changes in the prescription opioid market. And the survey needs to use good questionnaire validation processes and rigorous methods to minimize misclassification, particularly differential product misclassification.

And I am not an expert on survey development, but I think this could potentially involve factors like the question format, for example, using a yes, no, don't know type of question structure, rather than asking a participant to select products from a long list or a series of screens. This would also facilitate assessment and management of missing data.

Pill photos may be useful for identifying specific products and formulations. And, the order in which products are presented we've learned may be an important aspect of minimizing differential misclassification. So, we might want to consider strategies like multiple survey versions with random or varying question order.

We would like to see probability sampling methods used possibly with over-sampling of high-risk groups. And we're also interested in discussing the feasibility of a longitudinal follow-up component, where you could actually assess changes in behavior over time in a fixed panel or cohort rather than just repeated cross-sectional surveys within a population.

And then, finally, at the risk of saying

something that is perhaps very obvious, I just wanted to point out that even the best new survey or newly developed survey prospectively collected data can't go back in time to collect data from 2009 or 2012. So, when we're thinking about evaluating ADF products that are already marketed, this may be a limitation of any new prospective data collection system.

Okay, I'll put the first question up and then we'll go ahead and start the discussion. Thank you.

DR. XIE: All right. So, the procedure of discussion is the same as yesterday. Scott here will help us keep track of raised hands. Our first question is: Let's discuss the feasibility, advantages, and disadvantages of modifying established national surveys to collect data for ADF evaluation.

DR. GOLDIE: Dr. Krebs?

DR. KREBS: Hi. You know, I think for, like, the National Survey on Drug Use and Health and Monitoring the Future, my issue with the nonmedical drug use questions is that I think they are so nonspecific that they're really swamped by the almost ubiquitous behavior that is normative in this society,

where people save opioids. You know, hydrocodone or oxycodone, acetaminophen that they've received from a dental appellant or something else, and then share that with family members and friends, or use it for a different mild pain purpose. You know, people save these things because they feel they can't get them when they want them later on. And, you know, if you look at the way the questions are asked, an honest answer for many of us would be yes on those questions without any intent to use them for an abuse purpose. Certainly, this isn't a specific doctor-directed purpose, but people feel they're using them responsibly on some level. There is not an intent to abuse them. And I just feel like the questions don't distinguish between that kind of very common use, misuse or nonmedical use, and the kind of abuse behaviors that, really, this group is interested in. So, I think adding some sort of specificity to those questions would be really important to try to make conclusions about ADF effectiveness.

DR. GOLDIE: Dr. Novak?

DR. NOVAK: Yeah, I think that's a great

point. I know that, I think NSDUH did a really nice job of addressing, at least to the extent that they could. My point or concern about using some of these national surveys is kind of an issue that we kept bringing up. You know, when you have new products and new product entrants, and some of these surveys have some pretty complicated suppression rules in terms of the reliability of the estimates. And so you might get some single cases and you can't really present the estimate, and so you have just a raw cell size, which can be not very meaningful. Then the amount of time it takes to actually modify the survey, because you think about it, you have to go through OMB, which takes many, many months, and then you have to train your survey interviewers. And so that could be two to three years down the road. And so then the only thing that could be used on some of the surveys if they have the fill-in-the-blanks, which I think could be kind of interesting, where you can at least use the unweighted counts to sort of keep track of some interesting trends. Or at least -- then in terms of Dr. Krebs' interesting comment about, you know, the attribution of

behavior, you look and see what they're actually calling the pills. I think that could be instructive, and I've looked at the NSDUH write-in data and it's interesting for prescription pain relievers. You get very specific questions like M13, which is the actual inscription of the pill. So, obviously somebody was taking the survey, didn't know what they were taking and they thought it was something, a pain reliever, and they looked and said, oh, it's M13, or whatever. Or they can mislabel as a benzodiazepine or aspirin or something, so, I mean, there's just a lot of variability. But my central point is I just think that that's going to be a very -- that early entrants is going to be a very difficult hurdle to overcome given these national surveys have to serve many, many different purposes.

DR. GOLDIE: Dr. Compton?

DR. COMPTON: Well, the surveys like the National Survey on Drug Use and Health provide a wealth of information about sort of overall use of a group of products that the sample size just falls apart when you start looking at specific, especially specific

formulations within a class. Even looking at oxycodone or OxyContin, specifically, that becomes sort of at the boundary of what's possible to examine. And it won't give you -- you know, there's a conflation of misuse versus what you all are describing as the problematic use. Misuse is a pretty broad category, and yet the goal of these new formulations is to reduce insufflation and injection. That's not queried, and even if it were able to be queried, I think the base rate is unlikely to be sufficient to allow you to look at it with any precision. I think you'll be swamped by false positives. You'll get as many false positives as you get real cases if the rate is too low.

On the other hand, it still may give you a good sense of sort of overall popularity or overall use. So that if you think it's going to create a change in population misuse patterns enough that it won't be as popular among drug users and the people that as an addiction specialist I take care of, then these surveys might be helpful.

I also would be very concerned about new products, that the rates are just unbelievably low at

the beginning, so they won't give you an early warning signal at all. It will be a very late signal of misuse from a sample of 70,000.

DR. MCANINCH: Dr. Miech, Dr. Brooks, Capt. Jones.

DR. MIECH: Yeah, so I want to defend a little bit some of the national samples. Let me start off -- well, I'll start there. Some of the issues that were raised, I agree, that there can be a definite lag time, and a big national sample is like a giant ship and it can be hard to change it quickly and put in new questions. That being said, I think it is important to point out the difference between a grant and a contract. So, a grant, like Monitoring the Future, we're sponsored by NIDA, which everything we do is largely in response to the data needs of NIDA. I just want to point that out, because there is a very high-ranking person from NIDA sitting at the table, five chairs down from me. And so with that in mind, one of the big advantages of Monitoring the Future that I think NIDA sees is that we actually can respond fairly quickly to new developments. So, around Thanksgiving

time we have revision -- a questionnaire revision meeting, and then the following November we'll have collected 40,000 surveys from a national represented sample of in-school students. So, we can get this stuff out pretty quickly within a year. But, again, that's an advantage of a grant. If you're working through the federal government, you have to go to the Office of Management and Budget; that can slow you down considerably. So, it's something to think about.

As far as the reasons for misuse or different types of misuse, that's very important. And so we have questions, did you take this prescription opioid with a doctor's orders or without a doctor's orders, which kind of gets at that, but perhaps not as in-depth as would be useful to some people. So, we also ask questions in detail, I think seven or eight questions about why did you misuse it? Was it to get high? Was it to have fun, or was it because you had pain? So, with this information you can actually start to drill down to some of that. Now, that being said, there are these limitations, as Wilson pointed out very well. When you start talking about individual products, you

get to very small sample sizes.

So, let me give you some concrete numbers. In 2016, among 12th graders, we have a survey of about 15,000 of them every year. About 5% reported that they had misused a prescription opioid in the past year, 2% in the past 30 days. So, 5%, we had 15,000 people, so 750 people actually abused prescription opioids in the past year. So, that is something to work with, you know? And if 5% of them are working with ADFs or have exposure to ADFs of some type, that would be 38 or so. That being said, that's probably not enough to look at anything in much detail. But if you start collecting over years, over a period of years, then you might actually have something to start working with.

So, that's just some of the points I want to raise. I agree with everything that's been said so far. There are definitely limitations. It's not the cure-all, a national sample, but there are certain strengths as well in terms of the generalizability.

DR. GOLDIE: Dr. Brooks, Capt. Jones?

DR. COMPTON: If I could add one comment to what Richard said. For the record, this is Wilson

Compton. One of the strengths of Monitoring the Future is in early warning, in that they can add what they call tripwire questions, which are just one or two questions at the very end of the survey to ask about misuse of something new. That was added for Provigil, for example, and it hasn't been misused by a lot of kids, but that was a concern when that was introduced not too long ago. And so that might be a way to -- for teenagers, to quickly ascertain whether there is a meaningful rate of misuse of new products.

DR. MCANINCH: Dr. Brooks and then --

DR. BROOKS: Yeah, this is John Brooks. So, I just want to take a moment to try and lay something out that I've been thinking about. Because in reading this question, it really made me come back to some of the first principles that we started the day with yesterday, when Judy was laying out sort of what our purpose was. And to me, at this point, based on the purpose of meaningfully reducing abuse, misuse and adverse outcomes, it's really a surveillance question that we're asking. We want to be able to detect if, when these formulations are introduced into the

marketplace, are they ending up -- how can we detect that they're being abused, misused or if there is an adverse outcome associated with them?

In terms of abuse defined as addiction, I think that the existing systems, like NSDUH, would be very good at detecting whether an abuse-deterrent formulation of a medication is entering the marketplace and people are reporting use around that product in a way that is reflective of what we think addiction is. But in terms of determining whether the drug is being -- - that the deterrent is not working, that the deterrent is being overcome, I don't think any of these are going to very sufficient to detect that because of the very small numbers of people who are engaging in the behavior where you were trying to overcome the deterrent.

When we -- from my area, when we want to find people, when we want to find out when something is being abused by the people who are trying to abuse it, we do the survey of the people who are being abused -- sorry, the people who are abusers. They are also being abused by the drug. But people who are abusing the

drug, and then watch that population to see, is the deterrent formulation coming into their universe of abuse?

And I might propose that one way of beginning to think around detecting that is to create a system where the denominator becomes people who are injecting drugs, people who are inhaling drugs, people who are smoking drugs. And then creating, getting your numerator out of that as being the number of people in that population who are now abusing my different formulations of drug, including the ADF formulations. It serves two purposes. First, you'll detect the presence of abuse of the ADF when it enters that population and, depending on how you collect the data, you can compare the prevalence of abuse of the different formulations.

The other advantage -- the disadvantage of this is it doesn't give you insight into why is the person abusing the drug? What led them to abuse? How did their abuse evolve? But to me that doesn't seem to be the first principal question being asked here. The first principal question is, are people overcoming the

deterrent and therefore abusing the drug in a way in which it wasn't intended, either an oral medication that is being injected, smoked or inhaled?

The other advantage of this is it also allows you to potentially monitor for side effects or adverse consequences. That among people who report using the abuse-deterrent formulation, you can then create surveys that ask them in greater detail about potential side effects or follow them.

Now, the real challenge to these is how do I create my denominator population in a way that is relatively representative so that it both gives me good point estimates of what I think is close to the truth of the actual number of people using these drugs, and also provide consistent data that allows me to monitor for trends over time? There are ways to do that. I wouldn't put that shortcoming as a reason not to consider doing the method. But I just wanted to lay out that that's the way I might think about approaching a question like this to begin with.

We do something like this in HIV. We have the National HIV Behavioral Survey, where we go out and ask

-- what we're looking for are what are the risk factors of persons in different risk groups that are leading them to potentially acquire HIV infection? And in this survey every year, on a rotating basis, we interview either men who have sex with men, heterosexuals, or injection drug users. And we ask them a lot of questions about what are you doing right now in terms of risk that might increase or decrease your risk for acquiring HIV infection? We also incidentally collect biological specimens, which is something I notice none of these systems, as far as I could tell, do, which is a difficult thing in terms of IRBs, you've got to store the specimen. But just something to consider if there was ever an interest in testing blood or urine to see what was actually in someone's system, since there has been a -- people have been saying that there is a paucity of biological markers. That is one thing to consider.

Anyway, on the cycle where we interview injection drug users, we ask a lot about how they inject and sort of what led to their injection behavior; how did they get to that point and are they

doing things safely? It's a -- it may not be the ideal survey and it could certainly be improved upon, and something like that could be tooled to address these sorts of questions, but it would require something very different. Let's see if there is something else I wanted to say. I think that's it.

DR. MCANINCH: Okay, great. Capt. Jones and then Dr. Crane.

CAPT. JONES: Just a couple of things on NSDUH. So, with the redesign, they do include information around motivations for misuse. So, you could look at people who were sort of self-selecting to say were you misusing to get high versus pain or sleep, or whatever. Again, it's going to substantially reduce your absolute numbers, so you're going to have issues with reliability and precision. You also can look at abuse or dependence, so operationalizing DSM-IV, to get to a group to sort of answer Dr. Krebs' concerns around the broad definition of misuse.

And I think this is sort of a long run game. You have immediate needs in being able to look at issues around products that you've already given some

labeling claims to, but you're moving towards generic ADFs. So, there is a long run game here for having surveillance systems that are reliable over time and are probably worth the investment. So, I wouldn't discard the fact that there are bureaucratic hurdles with revising some of the national surveys, because we need some quick data sources, but we also need some long-term data sources. So, I think that's specific to the NSDUH.

There are other surveys that you put up where in some cases it might be easier to add specific modules. Some of the CDC surveys have done that for other public health issues. They have not done that for this, but it's something that could be explored, and I know that we've looked at that around some of the pain-related issues over time. So, those are other things to consider. Thanks.

DR. MCANINCH: Dr. Crane?

DR. CRANE: I may have mentioned yesterday the National Hospital Care Survey, which is coming out of NCHS, and Carol DeFrances, to my right, is leading that effort. I'm not going to try to explain the whole

survey, but it is getting hospital-level data from participating hospitals, emergency department records, inpatient when possible, and the shift has been toward electronic health records. So, from SAMHSA's perspective, we're interested in ED visits related to substance use. So, similar to DAWN, the substance contributed to the visit either as the direct cause or a contributing factor.

To get this kind of -- I mean, I think many of us are familiar with ICD-10-CM, and how the drug categories are fairly broad, and how the categories aren't necessarily consistent. If you look in the F ones, which are the kind of psych drug dependence and abuse, the drug class groups are not the same as the ones you find in poisoning. So, what we're hoping, what we're trying to do is encourage hospitals to submit clinical notes. This is an optional part of participation in the survey, and then see what we can pull from there.

So far, not a tremendous number of hospitals are doing this, and we have a lot of work ahead of us kind of seeing, you know, what we can generalize from

what we do get. We're going to be doing validation. But I think if something new is showing up, if it's documented in the record somewhere, we should be able to pick it up. Now, I think this idea of making these ADFs distinctive in some way could help. Because, I mean, the person -- it isn't always the person coming in who is identifying the drug. It could be somebody, you know, a household member and so forth. So, I think that if it's showing up, we're going to try to find it. Obviously, millions of records.

One thing, though, that I haven't heard anybody -- and we're interested in feedback on this, because we're going to have to use natural language processing, and so forth. But one thing I haven't heard anybody mention is polydrug use. So, we know most drug-related ED visits, there is more than one substance involved, particularly if it's being misused in some way. So, I mean, I guess that's another question is, how do you kind of, you know, disaggregate that to figure out, well, this drug -- this formulation was in this visit; was it being misused or was it just, you know, part of, like, polypharmacy, you know, kind

of assessing that?

The route of administration may be indicated, particularly if it's a novel. I think I mentioned that yesterday. And we're actually going to be doing a validation study, and the other problem is drug-related visits are -- well, at least traditionally they've been a pretty small percentage of all ED visits, maybe 2% or 3%. So, how do we find -- how do we validate our methods to find them? And I don't want to keep going, but we're using kind of an algorithm based on ICD-10 diagnoses and procedure codes, and so forth. So, we know that we can narrow it down to increase our true positives. What we don't know is what we're missing, because there's no clear drug diagnosis.

DR. MCANINCH: Dr. Winterstein, Dr. McClure, and then I'll conclude question 1.

DR. WINTERSTEIN: I actually have something different to talk about. I just want to follow up on this real quickly. We are working with inpatient psychiatric facilities as part of a project for CMS right now, and I also had the opportunity to look at a lot of charts lately, and this might be another

population. So, you just talked about the population of patients who come into EDs with overdoses. In the inpatient psychiatric facility population, depending on the type of facility, the prevalence of substance use disorder somewhere ranges between 25% and 50%. It's huge, and those patients are assessed very comprehensively. I mean, the charts are, because these are psychiatric assessments, they are explicit about direct use and types and modes of direct use, because that is just part of what IPFs do. So, that might be another really interesting population to look at and to get information on abuse.

The other thing that I wanted to say is something that might be -- and that might be completely naive what I'm saying now. But something that might be very helpful and perhaps not too hard to add to any type of national survey would be two pieces: one, make them linkable. So, obviously, NHANES can be linked to Medicare MECS data. It might be possible to do something similar with NSDUH data, for example, which would have, from a pharmacoepidemiological perspective a bunch of advantages that would allow potential

validation studies of claims data or EHR data. And I recognize the limitations with sample size, but it's sometimes amazing what you can do with a few thousand people. So, validation studies as well as calibration approaches and, in particular, approaches for adjustment for external confounding and propensity score calibration type of method. So, that's one part. The linkage would be very helpful.

And the other one would be to add additional level of -- along the same lines, to add additional level of stratification that would look at health plan. And that could be as simple as stratifying the recruited population by Medicare or Medicaid or private insurance, because the Medicare and the Medicaid populations are, in particular, I think important. And having the ability to link the data to those populations also allows very comprehensive assessment of how reflective that sample population actually is from the source population of prescription opioid users, if that linkage was established. And that goes back to the discussion we had yesterday about effect modifiers in trying to see whether incidents estimates

from those studies are representative in any way or fashion. Because if we're able to establish a linkage to MECS data, or any kind of Medicaid data or Medicare data, that would certainly be permissible. And, again, sample size restrictions for sure, but to me it seems this would be way to achieve a sampling frame that would allow a slew of additional research.

DR. MCANINCH: Thank you for that comment. We have another session this afternoon on linkages, so we can talk a little bit more about that then as well.

DR. GOLDIE: Dr. McClure, your comment on question 1, please.

DR. MCCLURE: Yes. One factor I wanted to bring up, and Dr. Winterstein touched on this, is health plan enrollment for the patients. That could become an important factor. When we look at the various states, especially for Medicaid programs, the formulary can be a bias factor that's in there. It compelled me yesterday with some of the discussion we had to look at some of the formularies and preferred lists on state Medicaid programs. And when I looked at several of them, I see the ADF formulations on the not

preferred list. So, Medicaid patients are not upfront going to be able to have access to these medications, which can introduce a bias. When I look at our Quest data, when we look at misuse of medications and it matching what is prescribed with drug testing, we see Medicaid patients had a higher rate of misuse than Medicare or third-party payers. So, again, health plans, I think, can be an important piece of information to understand what's happening with the population.

DR. XIE: All right. I think we need to move on to the next question. Let's discuss the advantages and disadvantages of Internet-based surveys, both opt-in general population panels and enriched samples for evaluating ADFs. In particular, what are the potential selection forces and how might these affect the inferences that we can make?

DR. CONRAD: Hi. This is Fred Conrad. So, I have a few comments about web surveys in general. I happen to be a fan, but I think when it comes to opt-in, use of opt-in panels, we need to be very careful about any kind of population estimates. In fact, most

peer reviewed journals won't accept population estimates from this kind of survey without some sort of calibration study to assure that they are representative.

There are representative panels that can be used for web surveys. They are recruited through probability methods, like telephone, and they are provided Internet access if they don't have a device. But it seems to me this doesn't solve the base rate problem, which has been mentioned a few times, namely, that in either a nationally representative sample or an opt-in panel, the prevalence of the target populations that Mark Levenson outlined are too rare to provide reasonable estimates.

If the sampling issues can be solved, and I think that's a separate issue, but I think they can be solved, web surveys do provide a very attractive option. First of all, web surveys are relatively inexpensive, sampling aside. There is no additional cost per case. So, if the sample grows or if this is a longitudinal study, the costs are fixed of developing and implementing the questionnaire. And they are self-

administered, which means that like CASI and ACASI, which have been mentioned a few times yesterday, this promotes candid and honest responses to sensitive topics, as we're dealing with here. So, I do think web surveys are an attractive option, but I think the sampling issues are really the obstacle, not so much the mode of data collection.

DR. GOLDIE: Dr. Parker?

DR. PARKER: Jennifer Parker, National Center for Health Statistics. I think I mentioned yesterday that we were doing some extensive work looking at the Internet panels for our purposes, and so far the jury is still out on whether we will be able to use them for national estimates. But I will say my program has two different groups looking at these Internet panels. The mathematical statisticians that are looking at variance estimations and bias and the issues there. But we also have a questionnaire design program that is very excited about these Internet panels because they're using them to understand how people respond to the questions, and it gives it some of the topics here. So, are people interpreting the question of use or

misuse or abuse in the way you think they are? And if they answer yes to a certain base question, then a lot of probes can kick in really automatically that you wouldn't necessarily burden -- you wouldn't put all those on a national survey because it's just too expensive. But we are -- they are definitely excited about using these Internet panels for understanding what different populations think about different questions, and I think that could be very useful here. Again, I don't know the details, but if you're interested you should contact me.

DR. GOLDIE: Dr. Novak?

DR. NOVAK: Yeah, I think all the points raised are really great. And I think the other thing to kind of keep in mind is that a lot of people think of these opt-in web panels as being completely convenience samples. And there's ways of basically taking them and using, like, methods of quota sampling and bin sampling to sort of fill population quota to come up with your original, you know, sample that looks kind of similar to the construction of, let's say, the United States population. Now, that doesn't account

for obviously the selection bias, I mean, because you have people that get onto the Internet, then you have another selection bias of people that have to opt-in to the panel. So, there's all these little different steps, but, again, there's a little different tweaks that you can use. So, for instance, we did a study where we actually supplemented an Internet panel with a market research firm, and these firms are available all over the country and they're in malls, and they kind of go anywhere. And so we said, well, we're really lacking in our low SES populations, and so we put them in lower SES areas, and they did basically street intercept, and we found some remarkably efficient ways of getting these people into the panel. Like, we would have the station set up for them to take the surveys right then and there. And it was, you know, obviously the variance estimates are never going to be as good as probability sample, but for our purposes it was a pretty good, quick and dirty estimate of sort of a mean prevalence of an early entrant of a new drug that was coming on the market.

DR. GOLDIE: Ms. Cassidy?

MS. CASSIDY: Hi. I just wanted to comment a little bit more on the sort of Internet surveys and the opt-in panels, I think, and maybe just relate it back to some of the experience that we had with the study that we did around prescription stimulants. And I just -- I agree with the comments that were made by the other panelists. And I also wanted to just give credit where it's due. I was standing on Dr. Novak's shoulders a bit when we did this prescription stimulant study with the opt-in Internet panel, and at the time it was somewhat novel to kind of go an Internet panel like that, an opt-in panel. I was -- I didn't have access to a large population base sample that I could draw from, so I had this particular -- I just want to echo Dr. Novak's comments that this particular group was really doing political polling surveys and hadn't really thought of looking at a health-related question at the time. And it was related to the question -- so, there was a bit of a proof-of-concept there if, when we did this, and we were able to create a sample that would represent the US population, would that have consistent estimates that would match what the study

that Dr. Novak did, and also the NSDUH data. And it did reasonably well. The other element of that was that at the time we did that study, Vyvanse was newly in the market. It's a prodrug formulation, and wanted to be able to see if we could get down some information from this type of a survey sampling effort that was more product-specific and could contain route administration data. And we were successful in doing that, and it was, you know, at the time it was a low volume drug. We weren't sure how much we were going to be able to pick up, and so I think still there are those issues of maybe precision in estimates. But I do think that there is a place in utility for certain types of questions and maybe taking the temperature on those questions for certain types of populations. I think some of those hidden populations are certainly going to be harder to get at with something like an opt-in panel. But if you're looking for, you know, efficiency in terms of data collection, we were able to have a sample of 10,000 individuals. I think they collected the data in two weeks.

And then thinking about enriching that with

some of these other types of mechanisms for -- you know, we couldn't look at adolescents, obviously, in these panels, so there might be other options for that to sort of enrich them. But I think that they could be useful in relating to the question for ADF. We used pictures, so similar to what some of the other surveillance systems were doing to be able to identify the pills and things like that.

So, at least at that point there was -- I think there is definite utility for those types of approaches, and they could adapt to the opioid scenario.

DR. GOLDIE: Dr. Green?

DR. GREEN: In development of the RADARS system nonmedical use of prescription drug survey that Jana mentioned, it's interesting to hear all these comments, because it's very useful, I think, as we look at future design and getting the best of the data systems that we possibly can. So, I did want to -- I think the same point is very important here, and recognizing that we can sample according to the population. So, we do diversify our sample by region

and then also by gender to make sure that we have appropriate representation geographically and some demographics. And then I think there is utility in maybe using the NSDUH data to benchmark or do that external validation of the sample that you are getting from the online surveys. So, we've looked at that as well. And pretty impressively the age groups matched up really well. The ethnicity was not as diverse in the opt-in panel as it is in the NSDUH sample. And then also when you start looking at that nonmedical use, recognizing that the definitions are a little bit different, we saw comparability there as well. So, in our program we ask about lifetime use of the products. For instance, opioid lifetime use was about 62% of our sample, and I believe NSDUH is 67%, so very comparable there. And also when we -- if they indicate lifetime use, so to Dr. Parker's comment that skip logic is great because you can drill down into those populations that are giving you a positive response for something that you want to study. So, if they indicate lifetime use, we then ask about the nonmedical use: Have you used it without a doctor's prescription or in a way

that is not recommended by your doctor? And then when they yes to that, you can ask the motivations. We asked is this to treat pain, is it to get high, other reasons, route, and all product-specific information. So, I think -- I definitely heard the comments about the low market share. And when we have these products that are not widely distributed is this going to be a valid estimate product level? I think this goes back to yesterday's conversation about drug groupings. So, can we at least look at ADFs as a group and look at that behavior.

I also liked John's comments, too, about looking at those that have the behavior, because you can, then, take that cohort of people that are reporting, even chewing of the medication. So, we were surprised to see that, you know, of those endorsing nonmedical use of opioids, 30% of them report that they chew an extended release product.

So, you can look at the chain of behavior, the snorting, the smoking, the injection. And then of those, and I think this goes, also, to Dr. Ciccarone's comments yesterday about are we looking for those that

are the blips or the signals of all of those people that are reporting injection or snorting, are ADFs showing up in that group of the people that you're monitoring? And also recognizing that this is a general population, so we don't expect -- you know, this isn't the high-risk group, so we can still complement the, you know, the data with the treatment center data, where we are looking at the special vulnerable populations.

I'd also like the comment about content validation, and so making sure that the questions are being asked are being understood by the users. We're doing that in another clinical study with some pain patients, and so I think that's great to be able to do this as well.

And then I just wanted to make one other comment about the -- is there a way, then, to use these to tease out, to Dr. Schnoll's comments yesterday, the actual patients that are getting into trouble with their prescription opioids versus the recreational users who are reporting nonmedical use or abuse of all kinds of drugs. Because we also monitor stimulants,

benzodiazepine, GABA analogues, and, of course, I'm from Colorado, so marijuana -- a lot of that going on, and then other illicit drugs. And so you can start looking at and trying to parse out those recreational users from the intended patient population.

DR. GOLDIE: Dr. Crane followed by Ms. Bose.

DR. CRANE: I'm interested in knowing -- has to do with the selection forces. So, you've matched to, say, the United States population and gender and maybe region; how much do you get into income, household income? And, also, so I'm interested in kind of social factors that go beyond the, you know, age and demographic that could affect somebody's ability to do it or have the time to even do an Internet survey. And, oh, what was the other thing? And, also, are the surveys scalable? I mean, do you need to do it on a laptop? Is it easy to do on a pad or a phone? I mean, I think phones, smartphones now are pretty ubiquitous, so that would be an important factor. So, I guess I'm just interested in social representativeness of these.

DR. GOLDIE: Ms. Bose followed by Dr. Lo Re.

MS. GREEN: So, in response, yeah, we do

collect other demographic information, income, education and a couple of other things. Your second comment was -- oh, then we also do include the DAST-10 inventory, which is a validated measure to assess risk of substance abuse. And that's also interesting. I think another internal validation to, I guess, say the individual is more likely to endorse nonmedical use for whatever motivation due to higher DAST-10 scores. They tend to have more polysubstance abuse, as you mentioned earlier. I think that's really important and interesting to see, not just opioids, but then what is the relationship with benzodiazepines and opioids and even alcohol intake and whatnot? And you said one more thing.

DR. CRANE: Scalable to, like, mobile phones and so forth.

MS. GREEN: Yeah. So, currently the technology that GMI uses, that's our vendor that we use for the online surveys, they are working on the mobile compatibility version. They're having a little bit of difficulty with our survey, because it is pretty complex when you think about all the different products

that we ask about. Basically, they end up with matrices. If they endorse a product, then that product shows up on the next page with a matrices that tells us all the motivations that influence your nonmedical use routes. Also, where they got it. That was the other thing I forgot to mention is we ask the source of the drug, where did they get it? Did they buy it on the street or get it from their physician? So, ours is pretty complicated, but it hasn't yet been converted to be compatible with the mobile devices, but I think that's important, too.

And then to Theresa's point, too, we have, like -- we do two launches a year, 30,000 respondents each, and it does take maybe three to four weeks. So, I don't -- hopefully it's not impeding the completion of those surveys by not having that application. I think a lot of the complex ones are done online.

DR. CRANE: I think it might affect who participates. That's what I was getting at, yeah.

MS. GREEN: Sure, absolutely. And we see that in the StreetRx program, and actually Nab probably knows the numbers better than I. We did convert the

StreetRx, which is the street price site, for those of you not familiar, to be compatible with mobile devices. And do you remember what percentage of people -- it's 80% of people that are going to that website are using mobile devices. That's also a very, I would say maybe five data entry points as opposed to the survey, which might take like 10 minutes to complete.

MS. BOSE: This is Jonaki Bose. This is more of my, sort of my methodologist, statistician hat and less of the NSDUH hat. I think that the NCHS experiences are worth looking into deeply and understanding what they're talking about, and the fact that if variance estimation is something that we're interested in, then that's something to look at. And that potentially some of these panels are good at questionnaire development and methodological work, but may or may not fulfill the needs that you guys have. But that being said, the NSDUH clearly -- or any large-scale survey is not going to be nimble. Not just OMB clearance, but there is an issue of field time, questionnaire development, a whole ton of things. And given that, what options do you have? And if we are

going to look at Internet polling and convenience samples as an option, then what do you do? What do you look at? And I think some of the things to consider is that large numbers are not a sign of robustness. So, we just want to be careful that when we justify the size of our surveys we're not saying we have a lot of people and therefore it is good. I also think matching solely on demographics is highly risky, especially if you do marginals only, because you're not looking at any of the covariant structure within there.

And so in addition to doing that, I would agree that you benchmark to existing substance use, so your outcome measures of interest. So, if you're going to do a general population, then you look at any of the federal large-scale population surveys and you benchmark. And when you benchmark, you don't benchmark just for the national totals, but among subgroups as well. So, you're kind of going through and doing a series of quality checks, because that's the best we have.

And also, as talking about replicability, so not just do one survey but maybe do several surveys,

where you have a series of questions that overlap. And so you should, if the population is similar, for those series of questions get similar answers within acceptable ranges and measurement error.

And the other thing I did want to say is also that it makes us more nimble, you can maybe get a large number of people in a short amount of time, but there are still some key tenets to data collection that have to be maintained, such as the questionnaire quality, and developing good questions takes time. And so if we are going to invest as a federal system in these types of activities, then we have to think about, are we going to have a pool of questions that we've upfront developed that can be implemented on the fly? So, questionnaire development, for example, cannot happen on the fly; it's the nature of questionnaire development. So, do you have a methods panel simultaneously along with these where you do use an opt-in panel and do questionnaire development while you're collecting estimates? So, I think it's really a matter of maintaining some of the essential federal standards that we have to operate by that OMB outlines

in our statistical standards and the Principles of Federal Statistical Agencies just came out, I think, yesterday or the day before, but fulfill the needs of the Agency's nimbleness and more detailed data collection, those kind of things.

DR. GOLDIE: Dr. Lo Re, followed by Dr. Conrad, then Capt. Jones, which will conclude question 2.

DR. LO RE: Yeah, I guess I have concerns about the disadvantages of Internet-based surveys. I think potentially they could be valuable if you're interested in evaluating the behaviors who are prescribed ADF versus non-ADF opioids. And, again, I come back to the questions that you really wanted to focus on yesterday, which is really to understand the effectiveness of ADFs versus non-ADFs, and the behaviors that are occurring. And so where I think these kinds of qualitative surveys would be valuable is perhaps understanding the behaviors. However, I worry, although -- I worry about access to these Internet surveys. I understand many people have phones, but I'm also concerned about the willingness to even respond to

any web-based queries. And particularly you're going to go through all the effort of questionnaire, survey design. Are people who are more likely to abuse not going to have access to Internet surveys or be willing to respond? And I have questions, if you're going to get representative information about drug use behavior from these, or if they're even going to have the capacity to be able to respond if they're abusing drugs.

And I think Dr. Brooks made some really astute comments in saying that if you're interested in looking at the behaviors of people who are abusing, then certainly collecting cases of persons who abused and misused and querying as he had done and showed in the surveillance for the Opana outbreak. But I think I have concerns that really this is -- whether it's going to be worth the effort in getting valuable information on behaviors.

DR. GOLDIE: Dr. Conrad?

DR. CONRAD: Just to follow up on the last comment. I think this is a very good point. The concern about nonresponse bias is pervasive in the

survey industry, and in this domain I think the concern is particularly appropriate. But I do think that making -- my original comment was going to be about the use of mobile devices and Jody Green's experience. I do think it's essential to be able to implement any questionnaire that's distributed online on mobile devices. Because for many members of the population, I suspect an even larger percentage of the target populations under discussion, the only way they go online is on mobile. And so the kinds of issues that were just raise I think are particularly likely to be exacerbated if we don't have mobile questionnaires available.

DR. GOLDIE: Capt. Jones?

CAPT. JONES: Yeah, I'm just going to echo the last two speakers and just point out. I think in addition to the importance of the mobile access for probably certain high-risk populations, there is also geographic variation. And in more rural areas they may not have reliable access even if they have computers, and that's a disproportionately burdened population in this issue. So, I do think that's a potential concern

as well.

DR. XIE: All right, we'll move on to question 3, and after this question we'll take a brief break. Discuss the design strategies for minimizing misclassification, particularly differential product misclassification in surveys being used to evaluate ADF.

DR. GOLDIE: Dr. Schnoll?

DR. SCHNOLL: Sid Schnoll. I was involved in funding two studies that tried to look at that, and what we found, that when given a card with pictures of drugs on it, people who claim they had used a certain drug, 50% could not identify that drug on the cards. And so the problem of misclassification can be big. Dr. Scharman mentioned yesterday, in terms of somebody even identifying their prescription drug, if their given a generic form, often on the label will be the name of the branded product. And people, you know, as we said yesterday, it's like Kleenex. Every box of tissues is identified as Kleenex. So, it is a big problem and I think if we're going to move forward in identifying products, we can't just go and have

pictures and under it say what the brand is, because then people will identify it as such, obviously, but that may not be what they're getting. And certainly what happens on the street, somebody is told by whoever sells them the drug, this is X, the person says, oh, yeah, this is X, and they don't know whether it is X or not, and they don't know what they're actually using.

And now we are running into an additional problem of counterfeit. And if some of you have ever looked at some of these counterfeit medications, they are very, very hard to distinguish from the real product. Colors are close, have the same indicia on it, the shapes are very similar. It's a very difficult situation and I think we're going to have to be extremely careful in making decisions to decide whether or not a person is actually using the product they said they were using.

DR. GOLDIE: Capt. Jones?

CAPT. JONES: A couple of things. I wish Tracey Green was here, but maybe Theresa can talk a little bit about this. I remember having a conversation with her a couple of years ago, where they

did some analyses to look at the ability to identify specific products, and they found variation between more infrequent recreational type user versus those who had abuse or dependence. And the folks who had abuse or dependence did a much better job, and that would be as n of 1, that is also my experience, that, you know, very familiar with imprint codes and drugs of abuse and knowing what they were. And a variety of those products have social capital. You have people come into the pharmacy who say I want N357. You know, that's their preferred Mallinckrodt version of hydrocodone. So, you know, I think it's important to think about who might be identifying, that there may be better specificity among certain groups.

I think this is also a place where within reasonable resources you could do some work on looking at both different ways of presenting information, different orders of presenting information. You know, testing that out, so that if you do try to modify an existing survey or create something new, you have some actual evidence to inform those efforts.

DR. GOLDIE: Ms. Cassidy and then Dr.

Dasgupta.

MS. CASSIDY: And so I just wanted to expand a little bit on the comment that Dr. Jones has made. We did work with Dr. Tracey Green to look at some of this issue of misclassification particularly as it related to prescription opioid use, but OxyContin and Opana ER. Both of those products had been reformulated, and trying to understand when individuals who are coming into or being assessed for treatment, if they are able to identify those products and distinguish the difference between them. We were a little concerned about a continuation that we saw of endorsement of original OxyContin, and so wanted to understand better why some of that persisted, and was that in the way the question was being asked? Is that in the way that the pill or the image was being presented? Was it -- and so it was a qualitative study. It was a small group of abusers, but we did find that there was some differences in the type of abuser who was able to more specifically identify and sort of very confident and positive about -- and we used a couple different methods. It wasn't just sitting with them and showing

them cards, but, you know involved interviews and then following up with them. There was also an element of, you know, there was some element of, like, if they're sort of -- their sort of trusted partner, whoever that was, their sort of friend that maybe misused or abused drugs with, was saying, like, this is that particular product that they were using, that they would tend to endorse that even though that wasn't necessarily. So, there was some sort of level of confidence or differentiation for the different types of users.

What we did do is use that information to then help us inform what kind of, you know, enhancements we could make to the NAVIPPRO data that we were collecting, so that we could sequentially start to test that out to see if, when we changed something, and we did make some -- if people didn't respond to, you know, reformulated as, you know, the name of the drug. It was like old OxyContin, new OxyContin, old Opana, new Opana. So, there was some sort of standards that came out of that that sort of resonated with some. And I think that we could do more work in that area to sort of test that out with how we're collecting data and do

that sequentially so that we understand what the impacts are when we make some of those changes.

DR. GOLDIE: Dr. Dasgupta, please?

DR. DASGUPTA: I'll keep it short; because I think Theresa covered some of my points. But I think misclassification can be purposefully used as a method of social control, right? So, in relationships, in romantic relationships and close friendships, where one person is responsible for preparing the drugs, the tablets or heroin for injection, the person who is actually ingesting the drug may never have actually seen the tablet. And we see this happen -- I mean, there's gender differences and all these other things, right, so an amount of social control.

Bringing that back to how does that impact an actual ADF evaluation, I don't know how, you know, unless a particular drug gains a cachet enough that it's going to have -- differentially do that, have that kind of attractiveness, I don't really know how those biases in general would differentially impact one ADF versus another. So, while I think these are very important social and public interest questions, when it

comes back to like actual ADF evaluations, I don't know how much that -- how important that is.

DR. GOLDIE: Ms. Bose, please?

MS. BOSE: So, the more I listen to what we're talking about, I think that it may be of use to identify some of the methodological challenges that we're talking about, some of the measurement challenges, before we talk about survey design and things like that. So, for example, can respondents distinguish to the level of detail that you need to answer a given analytic question? And that might depend on the question. So, it's a -- you've outlined a number -- the large scope that we want to talk about, but every time I think about the NSDUH and what it can do, or what some of the other data sources can do, I start drilling down to the specific types of analytic questions we're talking about. So, I think it may be useful to kind of step aside and say here are the broad to the detail type of questions that we are looking to answer. Based on that, here are some of the methodological challenges we have. Can respondents -- does the ability to identify a given pill vary

depending on frequency of use, the presence of a substance abuse disorder? Because if we're doing a survey of a general population, then all questions need to be understood by every single person answering them regardless of their substance abuse data. And an example that we often talk about is when we're developing general identity questions, a lot of times I've heard, well, the person will understand it if it applies to them. Well, it doesn't matter; it still needs to apply to the 95% of the people for whom it may not apply. And I think similar considerations apply to the nature of use, route of administration, all of those kinds of things. So, I think maybe coming up with a simultaneous methodological plan that supports your analytic goals and then feeds into overall survey design may -- it's expensive, it's time-consuming, there's always staffing and resource pinches for us. So, this is an ideal approach potentially, but I think it may be helpful for us.

DR. GOLDIE: Dr. Boyer?

DR. BOYER: Yeah, so the Internet isn't just populated with drug users, it's also populated with

tricksters who do things like send out stuff like fake news. And one thing, like, Theresa, I don't know how you ensured internal validity of your, you know, like of your sample on Bluelight, but the psychotropic drug user population are famous for being tricksters. So, I always, like, when I did my online surveys of drug users as far back as 2006, I mean, one of the first things I did was start building in a number of questions about fake drugs. And if they had used the fake drugs, then they tossed the stuff out.

So, I understand that people like to get lots of surveys and you want everybody that you contact to complete the survey, but that's not a reality online. It will never happen, I don't think, to any reasonable degree. And I worry about the quality of the data that you actually do extract from it, because people will just make stuff up.

DR. GOLDIE: Dr. Novak?

DR. NOVAK: Yeah, that's a great point by Dr. Boyer. I think we've asked some questions about fake drugs, too, in particular, Superval (ph) and Darnital (ph). And both we've gotten less than 1 percentage of

people that have endorsed those. And I think a little bit more people misclassified Superval than Darnital. I think they kind of figured it out.

But the point I wanted to make in my original comment was in terms of, you know, we've done some studies, and we have a paper in process now where we've asked abusers and nonabusers to identify different types of medications that are abused, ADFs, non-ADFs. And we found an interesting kind of artifact, that it's just not the person being an abuser and their consumption, but it's the actual consumption of the drug, which shouldn't be of any surprise to anybody here.

But if you have a new market entrant, like Zohydro, even Zohydro users were less likely to correctly identify that relative to some other drugs. And then there was also a seasonality effect that we picked up with regard to sort of a shift of identification with the Opana epidemic that happened in Scott County, where people during that time when taking our surveys they were more likely to misidentify. And traditionally, if they got the question wrong it was

OxyContin was the Kleenex. But during that time with the Opana outbreak in that period, the Opana actually became the new Kleenex. And so I think we have to be very sensitive to, you know, the secular drug trends and also the penetration, and how people can easily be sort of swayed by the media and whatever that's going on.

DR. GOLDIE: Ms. Cassidy, do you want to respond?

MS. CASSIDY: Yeah, I just wanted to respond to Dr. Boyer's comment about, like, how do we validate some of this Internet conversation or what's discussed on the Internet. I think there's a couple of things. One point is within our treatment center data that we're collecting, we also use fake drugs, and in the surveys that we do, we also include fake drugs. In almost all of those, every one of those efforts, there is an extremely low endorsement, you know, less than 1%. So, just a -- so, that's one factor, one aspect.

I think the other point that I wanted to make in relation to Internet surveys is, we keep, as a group, talking about the populations and what's the

population, or which segments of the population and what you can learn about those different segments of the population about abuse as it relates to ADF, and what data sources and methods are helpful in doing that. And I think that when we're talking about maybe opt-in panels, and we're talking about Internet service in the general population, that's sort of a -- that's one aspect. And the types of questions and the types of information that you can gain there is somewhat different from an Internet survey that would be looking at, you know, people who are recreational abusers or drug abusers who were discussing things online. I think as it relates to drug discussion forums, like Bluelight, you can watch what people are talking about passively and see what they're saying and what their behaviors and their perceptions and their attractiveness or beliefs are around particular products. And then partnering with some of those forums and communities you can ask them more actively some of these questions about their behaviors and their perceptions about these things. Another aspect of these communities is they tend to be somewhat self-

policing, so when there's bragging and really just wildly false information, they're pretty, as a community, they have their own sort of internal structures and rules about how they communicate and what they're allowed to talk about, and how they police that for themselves. So, we've worked with some of the moderators when we're talking, you know, we're thinking about an Internet survey and trying to make sure that when we're asking questions that those questions are focused and they resonate with those communities in a way that we can elicit that information. But in terms of the drug abuser population, doing those kinds of web surveys, I think those right now are really enrichment type activities where we could understand better about the phenomenon. And so things like are people trying to manipulate for a particular product, to come up with a new route of administration or extraction for something. I think there are different questions that we're asking of different populations, so we're not necessarily trying to have like the rigor of precision and valid estimates. That hasn't been -- to date, that really hasn't been the goal and the objective. I think

there is a place for that type of data collection and information that is important when we're thinking about trying to get at these more hidden populations who it's difficult to maybe elicit that information from.

DR. MCANINCH: I'm just going to jump in. We are scheduled for a break now, and to complete this discussion afterwards. But I think we have a great discussion going and I wanted to ask if people need a break now or if folks are okay pushing through for another 15 minutes or so, to finish this discussion and then take a break afterwards? I'm seeing some nodding, so we'll keep going. Okay, thanks.

DR. GOLDIE: Dr. Boyer?

DR. MCANINCH: And if anybody does need to leave for a moment, that's fine, too.

DR. BOYER: Yeah, I think the only thing I'd add to that is, depending on the population and the website that you want to -- website or websites that you want to draw from, having the buy-in of, in the case of Bluelight, either Sebastian's Ghost or Monica, you know, who could do the work would be critically important, too.

DR. GOLDIE: Dr. Brooks and then Dr. Miech.

DR. BROOKS: Yeah, John Brooks. So, looking at the question about designing strategies and minimizing misclassification, clearly it sounds like in all the different forms of surveys that people are using there is this chronic difficulty with misclassification, which is reducing your predictive positive value to know that when I say it's Kleenex, it's Kleenex and not Costco tissue. You know, thinking about ways to reduce the -- there are a lot of creative solutions out there. But one that crossed my mind but it is first a question to FDA is, to what extent does the Agency has jurisdiction to dictate the appearance of the tablet as its manufactured? Everybody knows the purple pill; everybody knows the little blue pill. And is there any way that you could require or encourage manufactures to create formulations that are distinct enough that people will reliably begin to remember them? And so that if generic formulations are made, they have to be distinctly different enough that users can remember them?

DR. THROCKMORTON: I'll just say short answer,

limited, pretty limited authority there. We would have to be able to decide it was a safety -- something necessary for safety or effectiveness.

DR. BROOKS: So, that's what I thought the case may be, and I was going to argue the issue here is that these are drugs that have a particularly bad safety profile in terms of abuse, overdose and death. And you might be able to leverage that to push for some changes in that area.

DR. GOLDIE: Then Dr. Miech?

DR. MIECH: I pass, thanks.

DR. GOLDIE: Okay. Dr. Crane?

DR. CRANE: I wanted to put in a plug for good ethnographic research, which is more than just asking people questions. It's -- there are methods to do this to validate it, and also its participation. Because what, as many of us know, people tell you may not reflect what they actually do, and that could be for a variety of reasons, partly because they want to tell you what they think you want to know. And then, of course, of it's illegal activities, there is a reason to conceal that. Participation doesn't necessarily

mean you have to use drugs with them, but it's being around people enough to see what actually happens.

And then the time element is really important, too. Now, this is -- oh, Wilson is not here. It's not something to be done quickly, and it's not something that maybe has large generalizability, but as one of my professors at Cal used to say, it's highly -- you know, limited generalizability but it can be highly valid.

DR. GOLDIE: Dr. Dasgupta? It's been covered?

DR. DASGUPTA: But I think the questions about, yes, people make things up online, people make things up in real life, people make things up on paper forms. I mean, I don't think the problems we're talking are at all specific to the Internet. There is literacy bias; there is all these other issues there, right? So, I mean, I think if we -- I don't have the hubris to think that the data we collect is 100% accurate in every questionnaire. And I think the methods to -- and the nonhealth Internet survey field is very -- has a huge kind of body of literature which deals with these problems, whether you're talking about car color preference or what kind of socks you wear.

And there are statistical methods, there are kind of survey structure questions that you can do to get that information and have an idea of what's valid or not. And I think the same applies to any of the household survey -- sorry, not the household surveys -- any of the surveys we were talking about, whether they're federal or not, that you're going to get an element of, yeah, this is BS. And you have to know that it's going to happen and have to have a way to address that upfront. I mean, I don't, you know, there is no other way to do it.

DR. GOLDIE: Dr. Ciccarone, I wanted to give you an opportunity.

DR. CICCARONE: I just wanted to build on the quick comment by Ed Boyer a minute ago about getting buy-in from these online communities. There is increasing concern among them about how researchers and other entities are interfacing with them. They're building their own internal community-based ethic, and stuff like that, and it's important to play well with them.

DR. GOLDIE: Dr. Crane, you want to follow up?

DR. CRANE: I was just thinking that, I mean, in terms of doing ethnography, it's not so much I'm trying to figure out what the objective truth is, but what people decide to say to me, is it in itself meaningful? They may tell me one thing because, you know, as a white person they think, oh, you know, she's thinking -- you may be seen as representative of the state or of a dominant ethnic group or so forth. So, it's not so much -- I mean, I think it's going beyond just kind of trying to figure out. It's not the same as doing a survey whatever the answer is. It's understanding the meanings of what people are actually saying.

DR. GOLDIE: Dr. Conrad, did you want to contribute? Okay. Then, I'm sorry, Dr. Schnoll?

DR. SCHNOLL: Sid Schnoll. I just want to reinforce some of the comments that were made about ethnography. I think it's a tremendous way to collect very important, detailed information that you really can't get any other way. And, yes, the numbers may be small, but they can be very important in terms of the kinds of data that are collected. And I know Wilson's

not here, but I am concerned that I don't think NIDA is supporting ethnography studies the way they used to, and they should get back to it. But I just want to also reinforce something that Scott said about people not endorsing phony drugs. When we started RADARS, we put in a phony drug that we called Cebadone (ph), and it was very rarely endorsed. But when one of our ethnographers was out on the street, one of the questions they often ask: Are there any new drugs around? And a number of people said, "Well, I've heard of this drug Cebadone, but I haven't seen it yet." So, I think putting things in there can create certain biases that were unintended.

DR. XIE: Well, I think we have 10 more minutes to discuss the last question. We'll skip question No. 4. I think we covered a lot of it. So, the last question is: Discuss the feasibility of using Internet or other types of survey panels longitudinally to evaluate ADFs.

MS. BOSE: I think a lot of longitudinal work depends on your analytic goals, and I think for me personally it's a little hard to discuss the

feasibility of using a longitudinal panel without knowing what your analytic goals are. But my experience on longitudinal studies and designing longitudinal studies is that they are sample size heavy, because the number of pathways and trajectories, if you're trying to map a number of different things, then your sample size does get pretty large pretty fast. If you have a series of repeated measures that are fairly simple, then maybe it wouldn't happen.

So, I think that -- so, for example, some of the mental health studies that I've worked on designing have to do with mental health and the onset of disease and the remission and the reappearance. Those things are really, really sample size, so then you kind of go, okay, maybe our analytic goals don't require a representative sample. Maybe it doesn't require a nationally representative sample. Maybe a nonrepresentative regional sample combined with other qualitative or ethnographic features will help us answer some of the detailed questions we're looking for, but they're longitudinal with several waves are nontrivial efforts.

And then just to talk about -- actually, it comes up later, the follow-up surveys. Does that come up later somewhere in the agenda? Okay, those are a little bit different, because the National Health Interview Survey has modules. On the NSDUH we have done some, so those we can talk about later.

DR. GOLDIE: Dr. Green?

DR. GREEN: I think a, I guess the word, the buzzword these days is omnichannel. So, doing these longitudinal surveys doesn't mean they all have to be online. You can use texting, you can use other modes of communicating with the people you're trying to follow, you know, that might be a quicker response so that you can hopefully retain those same individuals over time. And, of course, as mentioned before, if the initial survey takes 10 minutes, you may want to have an abbreviated survey to follow it from that period forward. But I think it is a great way to assess both the exposure to the product, so have you gotten a new prescription? What prescription was that? And being able to track the opportunity for exposure and then what the actual experience was with that product. I

think one thing that needs to be said here is it's great to think that these patients are just getting one product and I'm going to follow them in their experience on that one product, but that's not reality. And there are many people around the table that can speak to this more succinctly as clinicians than myself. But my understanding is these patients are not just having an experience with one product; there's rotations for different pain medications. So, to be able to follow them in their experience, making sure that we understand what that opportunity of the exposure was, what prescriptions they're getting, and then being able to relate that experience.

And then just the last thing for consideration, I don't think it's a deal-breaker, but the anonymity is something we haven't talked about. So, with the online survey for us, it is anonymous, and we don't have a way to identify the participants. So, we do see probably, maybe, I would like to believe pretty honest answers, for the most part, about their experience and what they're doing and the behaviors with these medications. And so just making sure we

balance the ability to maintain the anonymity, because they do, again, these are aberrant behaviors, they need to make sure that there aren't going to be consequences for revealing what they're actually doing with these products. So, balancing the anonymity with the ability to follow them all the time.

DR. GOLDIE: Dr. Novak?

DR. NOVAK: Yeah, I want to actually pick up on the point that Jody just brought up in terms of anonymity. One of the things, in terms of building successful longitudinal tracking, which a lot of people is sort of 80% as the benchmark, you have to have excellent rapport in brand recognition with your research participants. And if you don't, they're going to -- I mean, to track abusers especially over time, you need to collect some pretty sensitive information. Abusers, they are very mobile, transitory, they move around, they move to different places. They switch cell phones, they can even switch email addresses, and we've gone so far as to actually, in our longitudinal research studies, to ask abusers to write letters to people that we can give to friends of theirs who --

here's to contact if I'm not using, who can find me. And then they can say, okay, here's somebody you can contact who probably knows where I am when I'm using. And so, I mean, those are all -- that's a lot of investment that are tradeoffs when you use these web panels and really web surveys in general. You sacrifice that connection in exchange for the efficiency that you could get with just getting a lot of data fairly quickly.

DR. GOLDIE: Dr. Winterstein?

DR. WINTERSTEIN: It also touches on the point that Dr. Green just made. I was thinking about the underlying population and where it would make sense to have longitudinal follow-up. So, samples that draw from the general population probably have too small of a numerator of opioid users that would lend itself to follow-up, and I'm not sure that's the best allocation of resources. And then, likewise, surveys that look at abusers and the mode of abuse. I'm not sure how much follow-up there is really needed, because we have already the mode of abuse there, and I don't know how much longitudinal follow-up would be really valuable in

that scenario. But where I could see great value is patients who are chronic opioid users and perhaps still in a usual prescription type of framework. So, for example, patients who were just initiated on some earlier opioid or who were sampled based on one year of exposure and then starting that follow-up to see how these patients developed into abuse pattern. That, to me, would be the most valuable piece of information.

DR. GOLDIE: Dr. Boyer?

DR. BOYER: I think there also needs to be a certain degree of stability in how to reach people. I mean, Drug Buyers -- Drug Buyers was a website like in the early 2000s, where you would go to buy OxyContin online and it disappeared after about 2008 or so, 2007 -- 2009. Even AlphaBay, you know, like, AlphaBay went down two days ago. Maybe it's related to the raid in Quebec, maybe they're trying to move to another site because their admins are still posting on other sites. But if you're going to try to recruit to other individual websites, you've got to make sure that it's going to be stable enough. And even if you try to move to something like Erowid, to try and pull people in,

like Erowid is pretty heavily edited, and Earth and Fire are increasingly cagey about who they work with. So, there's some real issues in terms of feasibility, and, like, maintaining access to a specific population.

DR. GOLDIE: Dr. Conrad?

DR. CONRAD: Just two comments. One is, it seems to me that real anonymity is virtually impossible to guarantee in a longitudinal setting. I mean, you just kind of have to know some identifying information about the participants to continue to recontact them. But confidentiality is not impossible to assure over the period of time. So, I agree with the earlier comment that establishing trust in the participants is, I think, crucial.

The other comment is, I wanted to endorse Jody Green's suggestion that this be -- I'd never heard the phrase omnichannel, but in my world this is called mixed mode surveys. And I think to maximize response rates of participation over time, you want to give the respondents as many ways to participate as possible. And I strongly want to endorse text messaging. We've done a number of studies and text messaging has great

properties, mostly because there is so little information about who is on the other end promoting candid responses. And also because it's asynchronous, so people can take their time to answer; they're not under -- even more conventional web surveys create a certain amount of temporal pressure to give an answer right away.

The one concern I have, and this just comes with the territory with mixed mode surveys is identifying mode effects. So, if there are differences between the respondents and text and web, is it because they're really different or is it because of the mode?

DR. GOLDIE: Dr. Lo Re?

DR. LO RE: Yeah, I actually think that longitudinal surveys are important and would be feasible for the overall goal of, I think, understanding the incidence and the risk factors for abuse and misuse. I think insomuch as wanting to understand the behaviors of misuse and abuse of ADF versus non-ADF drugs, longitudinal surveys would be valuable, although I don't think necessarily the Internet for the reasons that I mentioned before. But

we've already highlighted the current limitations of existing surveys, that they don't include information on injection, noninjection, drug use, alcohol consumption, other medical comorbidities, other drugs, the duration, the type of pain, their insurance. And it would seem like those are the only things that you could really get from asking the patients. And that certainly would go towards the risk factors.

I also think that we haven't talked about surveying the providers themselves who are prescribing the ADFs or non-ADFs, and it's not clear to me why some providers may prescribe a patient an ADF versus a non-ADF formulation. So, I do think that longitudinal surveys will be helpful, perhaps coupled with other methods, you know, with harder outcomes, like death, like overdose, perhaps in cohort studies.

DR. GOLDIE: Dr. Miech?

DR. MIECH: Yeah, looking at the question, I see there is a focus on Internet and other types of surveys. And kind of building on what Dr. Lo Re was saying, there are administrative approaches, using administrative data that I think might be really

helpful here, like PDMPs. I think we realize what the limitations of those are, that not everybody who becomes opioid abuser was prescribed those drugs. But nevertheless there are some other types of data sources I think that could really inform the question here. And we could look at maybe clinical sample size, too, kind of building on the idea of the providers and follow those individuals over time, recognizing limitations there.

DR. GOLDIE: Ms. Bose?

MS. BOSE: Again, two methodological points. The first one is what Fred just said, talking about mode effects. Mode of facts are real. Mode effects may -- the level of error associated with the mode effects may be ignorable, but that's something we might want to determine. And it's shocking how much the mode does make a difference. And so when we moved our basic demographic, marital status question, for example, from ACASI to CAPI, we saw a difference in missing less rates as well as in the estimates themselves, and this is supposed to be a factual question. And so there are a number of factors that affect modes, the number of

theoretical constructs whether face-to-face has a theory of reciprocity versus anonymity versus -- you know, there's all sorts of reasons, but they do occur. And we might, then, determine, well, we're just going to go ahead and mix the data from the different modes, but it's a more deliberate decision.

And the other point that I wanted to bring up is I don't know what laws govern the ability to keep your data confidential, but that's something to also keep in mind, under the federal context. So, for example, there are a number of agencies under -- that have been designated as federal statistical agencies or units under a law called CIPSEA by OMB. And so when the NSDUH data are collected, I can get a FOIA request and I can turn it down. I can be subpoenaed, I can turn it down, but the only reason I can do it is because I have a specific law that exempts us from FOIA requests. And so if FDA has something similar, and it doesn't have to be CIPSEA, it can be other laws; then, yes, you can guarantee confidentiality. But if you do not have such laws and you are vulnerable to different type of requests, and it can be actually internal or

external for us. It can be a GAO request; it can be an IG request. And so understanding the confines of your law will help you determine what it is that you can promise your respondents.

And then pushing that one level further, and this might come up in the linking one, but it applies to the confidentiality and response rate and data quality domains as well. On the NSDUH we don't collect social security numbers, the last four or the entire one, and the reason being is we are concerned about the adverse effect on our already dropping response rate. So, those are the kind of tradeoffs. And it might be easy to ask them, but there are consequences for collecting it. So, those are some of the things to kind of consider the tradeoffs, the benefits to linking with other data sources, which we would love to do, but --

DR. GOLDIE: Dr. DeFrances, please?

DR. DEFRANCES: I just wanted to follow-up on Dr. Lo Re's comments about surveying providers, and I know Dr. Scharman mentioned it yesterday. But we have a mechanism at NCHS called the National Ambulatory

Medical Care Survey. It's a nationally representative survey of physicians and community health centers, and that may be a mechanism that we can get at some of these questions. That survey was used in the past to look at antibiotic prescribing, and I just wanted to throw that out, that that may be a mechanism. And also in light of the commissioner's comments about training, the survey has two components. We do an introduction where we ask the physician opinion questions and about how they operate the office, and then we go in and we take a sample of patient visits. So, I wanted to throw that out for consideration by FDA as well.

DR. XIE: All right. I think some of us cannot wait for a break any more, specifically, me. So, let's reconvene about at 11:00 for audience discussion, and then the session will end. Thank you.

For the last session we did have a very lively discussion and I feel bad that I have to cut some of you off. But please feel free to use the docket link to sending your input, and also you can email us, send us any comments that you have in mind.

Let's start the audience discussion for the

last session. We're now going to begin the audience participation. Please try to focus your comments on the session's topic, which is building on established national surveys. You will be given three minutes to speak. A light system will be there. Green means keep going, yellow means hurry up, one minute left, and red means please go back to a seat. So, every speaker, please provide your name, state your disclosures, and provide your comments.

DR. COPLAN: Good morning. Paul Coplan, Purdue Pharma. I just wanted to share some of the work that we have done in case it would be helpful. So, it seems like the themes from the discussion this morning were that it is important to have nationally representative samples on the one hand and then Dr. Brooks mentioned doing focus studies in communities of high risk people, people abusing product, to look at the entrance of the product into their community to see the uptake in the patterns of abuse in the abuse-deterrent formulation. Then there was -- several people mentioned ethnographic research. So, the complementation of the smaller focused, in-depth,

qualitative research with the national surveys. We had planned to do that and in fact included national survey -- well, national surveys as well as an in-depth analysis of a focused cohort in Kentucky. The study was done by the University of Kentucky. It was published by Jennifer Havens, and the qualitative research was done by another person to complement the national surveys. And unfortunately we wanted to do it longitudinally, but by the time we got the survey going the product had already been introduced, so we could only look at the recently after the introduction. So, I wonder if that would be a useful example to perhaps this kind of combination of the national and the more focused abuser cohort. Thank you.

DR. HENNINGFIELD: Good morning. I'm Jack Henningfield with Pinney Associates and Johns Hopkins School of Medicine. Most of the discussion is on the -- how we track abuse and whether the AD opioids are deterring abuse. A different issue that I think is trickier but that I'd like to put on the radar screen, maybe the RADARS screen, is the utilization of these products by people with pain. And part of the

rationale we make sometimes is that, for example, somebody that is in a situation, a living environment where they are especially susceptible to theft, that it would be great that they be on these products. When we had one meeting, public hearing on AD opioids, I think the Veterans Administration representative said he wasn't sure that they should be paying for AD opioid because most veterans, he said, didn't abuse them. I think we've really got to be tracking how they're used and if they're actually helping people with pain. And what makes things a little bit more complicated is that at the same time we're introducing AD opioids, we're introducing new restrictions on how medicines can be prescribed and new burdens. And I think that they can disproportionately hurt lower income people and minority people, the very populations that ideally AD opioid would be helping.

I don't know how we track that; I don't have a clue. But I think we need to be figuring out of they are providing the benefits that they should be providing and if they're not, what we need to be doing to help them help people with pain.

DR. LEE: If there is no other audience participation, then we're going to move onto the next session. Dr. Tamra Meyer will give you a brief overview about this session. This session is about designs that assess exposure and outcome in the same individuals over time. So, here we're going to focus on cohort designs as a new opportunity to evaluate the impact of ADFs. So, she is going to give you a brief overview and then we're going to ask you some questions.

SESSION 6: DESIGNS THAT ASSESS EXPOSURE AND OUTCOME IN THE SAME INDIVIDUALS OVER TIME

DR. MEYER: Good morning. I want to make sure this is on, okay. So, I'm really excited about the discussion we're going to have, because I feel like everyone has been trying to have this discussion the whole time. And I feel like you've just been holding back waiting for this session, so it's going to be really good. Again, I'm Tamra Meyer. I'm an epidemiologist in the Office of Surveillance and Epidemiology in CDER. And Dr. Hana Lee will be moderating the session with me.

Okay. So, here's the overview. First, we're going to go over the causal question, and then we're going to go over the major challenges when we're trying to design new studies or use existing resources to do new studies. We've hit them pretty hard already, but they might apply to these types of studies a little bit differently.

Then, let's see, then I'll give you some examples of how these types of studies are being used currently. And then we've come up with five discussion questions. I think we're actually going to combine one of them, so stay tuned for that. And the discussion questions are around the challenges and how we overcome those challenges to design these new studies.

Okay, so here is a picture, some ideas about how the progression through the different routes and the development of substance abuse might go in some people. And this is not how it goes for all people, but in some patients there is this typical trajectory, and I think it's helpful to think about this when we're trying to decide which portion of effectiveness we want to capture. So, in some patients it starts with

chewing, or it starts with taking the formulation whole and then chewing and then crushing and snorting, and then in some patients or some people moving on to injecting the products. And someone might move through this trajectory trying to get more of the product out, or get the drug effects more quickly because of this increasing dependence on the opioid. So, this presents some opportunities to ask about effectiveness in different places here.

So, Dr. Schnoll is recommending that maybe we just focus on chewing or snorting, wherever the formulation is designed to work. We could potentially ask whether the formulations could help prevent someone from making it onto this trajectory at all, so any abuse. And we could also ask whether putting the formulation in there could help someone from escalating and moving on to severe substance abuse, or moving on to more severe substance abuse. All right, so there's lots of places to ask those questions and I could tell that you were struggling with this, as we do.

So, yesterday we were asking these causal questions using the ecologic study designs, and this is

where we were capturing the events in groups of people, different people across different time periods, and then normalizing those to some kind of measure of number of prescriptions or number of dosage units in the geographic areas. In this session we want to ask those same causal questions, but ask them in the same patients, so following exposure to outcome in the same patients over time.

So, like I said, we've hit some of these challenges before. To overview them we have that you have to sample the relevant populations, and I'll talk more about that in just a second. We have to get the appropriate sample size. We have to adequately capture confounders, choose the appropriate comparators, which can help somewhat with the confounding; accurately capture the exposure and the outcomes. And then I think this goes to Dr. Throckmorton's point, is that we need to choose a design that will balance the resource intensity and the time that is needed to conduct the study with our desire for the strong causal evidence that we need. Since there is this raging opioid epidemic, it's helpful if we can answer these questions

more quickly about whether these ADF formulations are effective, right? So, keep that in mind as we're talking through the study designs.

Okay. So, this has been a common theme, and here we were all talking about how the choice of the population is critical. And we might ask different questions in different populations, like whether we want to look at any abuse, or whether we want to look at moving to a different route of abuse. The question might be different depending on the population, right?

So, we've heard a lot about patients, like trying to track patients who are currently misusing and abusing opioids, so I kind of put them into one bucket. But then within that I just wanted to remind people that there are many subpopulations of interest that we might look at. Some of the ones that have been mentioned are patients with chronic pain, patients at high risk for developing opioid use disorder. Those are in both populations.

So, I just wanted to put this up there, because the choice of the outcome will differ, and the timing. I think we've already discussed that a little

bit, too, the timing of the outcome might different from someone who is in the first bucket and one who is not currently misusing and abusing to develop the outcome will be different from someone who is currently misusing and abusing.

Okay. The next challenge is the confounders. And Dr. McAninch discussed this a little bit, but the confounders are a little bit different when we're talking about these types of designs. So, I'll come up with an example of the exposure being the ADF opioid and the outcome being just overall abuse, but I could have picked anything.

So, we have some factors that are going to be associated with just the outcome, like genetics, and then we have a bunch of interrelated factors over on the left that are associated with whether or not a person has access to the ADF exposure. Things that we heard were street price, prescription price, insurance plan, which will determine a person's access but not necessarily the outcome. And in the middle we have all of these patient level factors in red that are associated with both the exposure and the outcome,

things like the social network or socioeconomic status, that we need to consider as potential confounders when we're designing these studies. And I'm not suggesting that these are the only ones or that we need to capture all of these. Our question for you will be to help us think through which one of these might be the most important, depending on the outcome that we select, or maybe some strategies at choosing the ones that we must capture if we're going to design a new study.

Okay, and I think this idea of choosing the appropriate comparators, and the counterfactual has also been covered. I'll just go through it quickly. So, the counterfactual would be this gentleman in blue, had he not taken the ADF opioid in his hand and potentially taken another opioid product without the ADF properties. And so we can choose a comparator to try and get as close to that counterfactual condition as possible. And so if we choose a good comparator, we might match the drug characteristics, like the active ingredient or the pharmacology of the drug, but then remember all of those patient level confounders from the previous slide. Choosing a good comparator we

might also be able to balance some of those patient level factors as well, like the indication, socioeconomic status, I mean, depending on which one we choose, it could be a good match and help balance some of those factors as well. So, we'll ask you to think through which of the characteristics of the comparators are important.

Okay, and this has come up repeatedly, capturing exposures and the outcomes is very difficult. For the exposures we have to capture prescribed drugs, other sources of the drugs, the product-specific drug is really important, and we've heard repeatedly that that's really hard to do. And then for the outcomes, we have to consider what the timing of the outcome is, like I said, depending on the patient population and where we think they might be in that trajectory. We have to try and operationalize these soft outcomes, like abuse, that get at intent, and that's really hard to do. And then we need to capture that route, specifically, abuse, to be able to ask questions about that trajectory that I put up there.

So, using our go to pharmacoepi data source of

claims, I just wanted to talk through some of the challenges with those data specifically. And as you've heard before, only prescribed drugs are captured. Often it's only prescribed drugs that make it through insurance claims, right? So, we might not capture the cash payments. We're definitely not capturing the other sources of exposure, but for the prescribed drugs, we might capture the product okay, because we have the product listed there in the claims data.

Let's see. For the outcomes we have to use algorithms based on diagnosis codes and procedure codes. And they may perform pretty well for hard outcomes, like overdose, especially if it can link to death data. But for soft outcomes, like abuse, they may not perform very well. And for route of abuse, I can't imagine a way to capture in claims.

Okay. So, for the study designs, the goal here is to provide a few examples that will hopefully help spark some ideas for our discussion. And I focused on cohort and case control studies, because I think we've adequately discussed the cross-sectional surveys. And I didn't want to bring in the self-

comparison studies because I think a lot of the assumptions for that study design are not met for our exposure and outcome. But if you have a different opinion, please feel free to bring it up. I just don't have any examples on those. And not all of the examples I chose are about ADF opioids, nor are they necessarily about the outcomes of interest here. But I think there are study designs that might be informative for our discussion.

Okay. And just a little disclaimer. Just by the fact of me bringing it up doesn't mean I'm endorsing the studies, and I don't intend to critique them heavily, but I will provide a couple of strengths and limitations as I see them, of the general design.

Okay. So, the first example we have is a nested case control study that was done in Ontario, Canada, and they looked at road trauma related to the dose of a recent opioid prescription, and they used prescription claims data to do this. So, they looked for patients with an emergency department visit, and then those are the cases, and then they matched them with patients without an emergency department visit.

And then they looked back to see if there was an overlapping prescription. Well, they had to have an overlapping prescription either at the time of the case or the matched control, and then they looked at the dose. So, they compared those two.

And as far as strengths and limitations, I think that it's pretty similar to like a retrospective cohort study using claims data, which I describe in a couple slides away. The only additional limitations, as I can see them, is that you have to do this careful selection of the controls to make sure they are also at risk of the outcome. And some of the techniques that we have to make the groups the same, so the cases and controls are the same, like propensity score matching, they're not well developed for case control studies yet. So, those are kind of the extra challenges for nested case control studies that I see.

This one is really interesting, and we're excited to have Dr. Brooks here and to get people's opinions about how we might be able to utilize these. So, the next one is this outbreak investigation design. And I think we are all aware of this example. But it's

kind of this case series followed by a case control design. So, in case you haven't heard about this study, this was a study to find out the exposure for an unusual number of HIV cases in Scott County, Indiana. And they did some interviews of the cases and found out that a lot of the cases had injected an ADF drug called Opana ER. And then they did a case control study where they matched the cases to close contacts, and then compared those who didn't have HIV. And they did questionnaires to ask about the typical HIV risk factors, like needle sharing and sexual partners. Anyway, this might be an interesting design for us to think about using on a bigger scale. I'm not sure how we would do that, but if we could be using HIV or hepatitis as markers of, like the failure of the ADF, like in this example. And it was something that Dr. Kornegay had mentioned yesterday; it's like these proxies for safety issues.

So, as far as the strengths and limitations, these designs are really good for rare outcomes that come to medical attention. And the limitations would be like the sample sizes were generally smaller, the

generalizability might not be there. It requires careful selection of the control group as well. And then as all of the discussion we've just had, collecting exposure information retrospectively, asking people to provide the product information might be difficult.

Okay. So, my example for retrospective cohort study design, Dr. Levenson already went over this morning, but briefly, one of the FDA-required PMRs, postmarketing studies, for extended release, long-acting, ER/LA, opioids, is to look at the incidence of overdose and death in patients newly prescribed an ER/LA opioid. And so this is done in claims data but also linked to mortality data, and Dr. Kornegay will go over linkages a lot more in the next session.

Let's see. The strengths of the design are that in something like claims you can get a large sample size, and for the prescribed products get accurate product information that are paid through insurance. And as I already mentioned, you're missing cash, you're missing outside sources of exposure, and then you have to rely on these algorithms to identify

the outcomes. But, of course, the mortality data also helps.

Okay. My example for the historical cohort study isn't quite an historical cohort study, but I wanted to use this example that one of our frequent audience participants did, Dr. Coplan did. So, this is a study that assesses the rate of doctor shopping, and this is a concept that Dr. Kornegay mentioned yesterday, too. It's like a proxy for abuse or misuse. And this study looked for patients who were using at least, or had at least two prescribers prescribing their opioid, and at least three pharmacies in a six-month period. And they looked before and after the reformulation of OxyContin.

So, in the older cohort, the historical cohort, they looked for patients who used the original formulation of OxyContin and then to see what kind of doctor and pharmacy shopping they had. And then they did the same thing in the current cohort and then compared them. And they compared the OxyContin pre and post, but they also compared OxyContin to other comparators, kind of like what we do for the ecologic

studies in the pre/post design.

The strengths and limitations are very similar to the retrospective cohort study. The additional one is kind of the thing we get into with ecologic designs, is the time related biases that might occur, since one cohort is completely in the past and the other cohort is, you know, current.

Okay. And the last example, I know we've sort of been talking about the whole time, is Dr. Degenhardt's study, and it's a prospective cohort study in patients who were misusing and abusing opioids already. And this study was designed to try and assess the impact of the 2014 introduction of the OxyContin reformulation in Australia. And they called it the NOMAD study, which I think is a great name, and they used questionnaires to collect data and multiple time points. And they collected data on route of abuse for both the pharmaceutical opioid and the illicit opioids. They asked about overdose, they asked about injection-related injuries and, of course, other things.

So, the strengths of these studies are clear, and I know Dr. Lo Re really wants to do these studies

already, too. So, we can capture opioids from all of the sources that we care about if we're designing a cohort study going forward. We can collect rich information on the confounders that might not be there in the claims data, like social network and socioeconomic status, things that are harder to collect in claims. We can also pre-specify and standardize our definitions of the outcome. The design limitations are that they are generally smaller sample sizes. Again, the same concerns about self-identifying the product, down to the product level.

Some other things that I thought of after Dr. Throckmorton talked this morning was just the speed of the study. So, maybe Dr. Degenhardt can comment on that in a minute about how long it took, because we have this concern about we have this raging opioid problem and do we want to wait 20 years to have results from a cohort study? Probably not. So, there's this idea of balancing the time that it takes and the resources.

But, anyway, so those are the examples. Hopefully, that will spark some discussion, and we'll

go ahead and start that now.

DR. LEE: Okay. So, the first question is, we are interested in hearing your thoughts on which populations are the highest priority targets for assessing the effectiveness and safety of ADF, or AD products?

DR. SCHNOLL: This is Sid Schnoll. I think one of the populations at very high priority are patients to whom the drugs are prescribed, what's going on with them, how they're using the drug. A study that I'm doing for another REMS, we actually interview patients to whom the drug was prescribed, and we get a lot of information. If you offer them confidentiality and anonymity, they will tell you all sorts of things. And you have the ability to follow them longitudinally because you know who they are. So, it does offer a great opportunity to look at things that otherwise you may not see, and it's an easy population to find. You can look up who was prescribed the drug, and we usually do that through pharmacies, national pharmacies, and they actually find the people for us, and they come and they're willing to be interviewed.

DR. GOLDIE: Dr. Brooks?

DR. BROOKS: I just want to ask, for this question, what do you all envision is effectiveness here? What is the effectiveness that you're trying to assess?

DR. MEYER: All of it. I'm sorry --

DR. BROOKS: I know it sounds a little facetious, but I think it's very critical to be super clear on what the question is that you want to measure, because that will drive what method you adopt to address the question.

DR. MEYER: Yeah, and I don't know if anyone else wants to comment on it for the Agency, but I think for me they're all important. Like, we can choose to ask about effectiveness at any place, right? And Dr. Schnoll was saying that let's care about the patient population to whom they're prescribed and look at what was intended to be prevented by the formulation. But then, also, I think of the, my personal opinion, of like public health interventions, too, and so we have to look why here as well.

DR. BROOKS: Because what I heard the first

day was the question we're looking to answer is how effective are ADFs at preventing diversion -- or preventing the abuse -- sorry, the drug being abused.

DR. MEYER: Yes.

DR. BROOKS: This is my normal vocabulary, I'm sorry.

DR. STAFFA: But I think we're very clear that through the route by which they are intended to deter it, so I think we were very clear about, that that's really the focus question.

DR. BROOKS: Good. Yeah, I just wanted to put that on the table so that everybody is thinking the same way, that we're looking at how to measure the effectiveness of preventing use through a route other than intended.

DR. SCHNOLL: I'm going to jump in here a second. These are abuse-deterrent formulations; they're not abuse-prevention formulations. And I think the language is very important here, because they deter abuse, they don't prevent it.

DR. GOLDIE: Capt. Jones?

CAPT. JONES: Just a further clarification

that are you are not concerned around effectiveness in the context of pain relief?

DR. STAFFA: That's correct. I believe that's determined at approval.

DR. CRANE: Sorry, just wondering what you were thinking in terms of safety?

DR. MEYER: For me, I think of the HIV outbreak, for example, and the idea that patients are moving along that trajectory, right? So, moving from potentially snorting it to injecting it and having more severe health outcomes. That could be one, like, safety signal, but I'm sure there are others.

DR. STAFFA: This is Judy Staffa. We did have a safety signal that I believe has been put into the OxyContin label where patients had some difficulty swallowing it because the coating or additives that were used to prevent it from being crushed made it sometimes difficult for patients to get it all the way down. And that was detected -- I believe it was reported to our spontaneous reporting system, and that information was added in the label. So, that's an example of a safety issue that could occur in patients.

And I think what Tamra brought up was a safety issue that could occur in people who are trying to abuse it through other routes.

DR. CRANE: So, there are some that you can kind of catch quickly, and then there's others which would -- you probably never could have anticipated without this research.

DR. GOLDIE: Dr. Brooks, did you have a follow-up? Dr. Krebs?

DR. KREBS: So, I'm going to agree that I think patients are a high priority, not the only priority, but certainly one, in part because these are the folks ingesting the medication and in some cases paying more for it than they would for a different product. So, I was going to say I do think there are some trade-offs in terms of what you can get from different types of studies. And if you're studying patients, an advantage of that, of going to the source and starting with the drug dispensed is that then you know what the drug is, so you clearly know the exposure. And if it's linked in a health system to outcomes, then you can be pretty clear on at least the

discrete outcomes, things like death or emergency visits, or hospitalizations, those kinds of things. But if you're linked to all those things, then I do think the sensitivity of the questions comes into play in terms of how willing people are to respond to your survey and to stay in a cohort longitudinally. I have a cohort in VA of more than 9,000 patients treated with long-term opioid for chronic pain, and I've been cautious about what questions. My primary outcome does not have anything to do with abuse, and so I've been very cautious about what kind of questions I include on that topic. Of those who have opted out of ours -- you know, we have about 66% response rate, and among those who have opted out, probably the biggest comment is they don't trust that it's confidential, or that this isn't linked to their clinical care. You know, patients are very sensitive right now to the general milieu in the society that people think people prescribed drugs misuse them and that misuse is the main reason why people have poor outcomes of opioid therapy. And so patients don't want to be associated with that and are concerned that data being collected

about how they may misuse drugs could be used, then, to take away their access to those medications for pain or any other purpose.

So, I'm not sure, it sounds like maybe you've used some different methods; you're doing more in-depth questioning about routes. But at least in my captive patient population in a health service, it's -- you know, I'm not sure we would get our response rates that we have, or have the kind of follow-up that we've got so far if we were asking a lot of really sensitive questions about misuse of the prescribed medications.

DR. SCHNOLL: This is Sid Schnoll again. We embed some things in a broader survey. I mean, you don't try to focus it on that area, but we were surprised at how open patients have been. But we make it clear to them that this information does not go back to their provider, so the provider never sees the information.

DR. KREBS: And is it a longitudinal survey where you're going to have re-contact with the same cohort of folks? Because that was my concern, too, was that maybe they'll answer it once, but will they come

back in a year and answer it again?

DR. SCHNOLL: We have some that have responded in a longitudinal fashion, but it hasn't been going long enough to really talk about.

DR. DEGENHARDT: If I can just also comment on that -- Louisa Degenhardt from Australia. The cohort that we created in Australia was we recruited people outside of the clinical context. And as I think I mentioned yesterday, some of them were receiving prescriptions from doctors; not necessarily one, it could be multiple. But we were very definitely recruiting not related to them being a patient or not a patient. But the way that we recruited people was, did you tamper with pharmaceutical opioids at least once a month? We asked a huge amount of data, and while it was very sensitive, we were still able to get a 92% follow-up rate at four months and 90% follow-up rate at 18 months. So, it is possible to have a lot of data, a lot of sensitivity and not lose people, I think, if you make sure that everything is very separate from any consequences, either clinical or otherwise.

DR. KREBS: This just goes back to our

conversation yesterday about who is a patient. Well, these people are all maybe patients and things are certainly overlapping circles. But if you want to get kind of that in-depth information about misuse or abuse going for that kind of population outside of the clinical context might be the best place to do it. And if you are more interested in sort of the broader population with fewer of the people who are doing things like tampering, but more detailed information about the drug exposure and potential hard outcomes, then going for that clinical population might be the way to go.

DR. GOLDIE: Dr. Graubard and then Dr. Lo Re, please.

DR. GRAUBARD: So, I just have a general question. I'm hearing various -- information about various cohorts and subgroups and so forth. What is the recruitment rate? I heard 66% response rate, but what's the actual recruitment rate and what is the retention rate? Because I suspect when you get into sensitive items, particularly in the United States, I don't know how it would be in Australia. Australia

sounds better than it is in the United States. I'm a little concerned that your retention rates are really going to go down quickly, and also recruitment rates. I mean, just in things we do at the cancer institute, we have difficulty getting people in cohorts, just the recruitment cohorts, and we're not asking the sensitive questions that you're asking.

DR. GOLDIE: Dr. Lo Re, please?

DR. LO RE: I'm going to comment specifically on safety and particularly comment regarding the HIV, hepatitis C, and other safety outcomes. I think in regards to the populations, this may be one of the situations where you want to take -- you could potentially use retrospective cohort studies to utilize electronic health records to assess incident HIV and hepatitis C. And I guess I'm thinking, at least in this country, both Kaiser Permanente and National VA, there have been studies that have merged both the data, and we published a study to look at the risk of acute liver injury associated with retrovirals by hepatitis status merging both VA and Kaiser. And I think certainly you have access to laboratory data which

could assess hepatitis C and HIV status. But if you included new users of ADF and non-ADF, it would allow you to evaluate incidence, incidence rates of those infectious outcomes, but also other outcomes. And I go back to Opana and the TTP, you know, other skin and soft tissue, severe skin reactions. Other potentially untoward skin infections from injection that potentially could be -- develop algorithms in those data sources and compared across different -- within classes, across classes, ADF versus non-ADF, to specifically assess safety.

DR. GOLDIE: Capt. Jones followed by Dr. Compton, please.

CAPT. JONES: So, I have a question, because as researchers, I think we're going to the place of people who are abusing substances and people who are addicted. And historically FDA's view has been more focused on the patient rather than nonpatients and diversion. I think under new leadership that seems to be shifting a bit and the decision around Opana reflects sort of a broader public health perspective. But I think FDA's perspective on ultimately why do you

want this information? What regulatory decisions will you be making? And are you making it in the context of a product being used as labeled, or a product not being used as labeled by nonpatients? And sort of what is the weight of the patient-provider traditional use of a product versus the public health implications of nonpatients using these products? And I think that also helps to inform, because I think we would naturally say let's -- the addictive population is much more likely to be manipulating these products, or attempting to manipulate these products than the vast majority of people who are legitimate patients with pain who are getting opioids. And the PMRs have largely tried to address some of the prevalence of the people receiving opioids, you know, what's addiction rates, overdose, death rates, stuff like that. So, I think it's important to understand the patient versus nonpatient perspective from FDA to address those questions.

DR. STAFFA: This is Judy Staffa. Well, I can take that on, but then I'd also love to hear from Dr. Throckmorton. I think it's both. I think the PMRs

you're referring to with a lot of postmarket required studies in this phase. The postmarketing required studies that are on the manufacturers of extended release, long-acting products, many of those have been referred to here today, were focused on patient populations to try to understand the risks in patients taking these products, all of these products, independent of whether they were designed to deter abuse or not. So, they had a different purpose than the PMRs we require from companies who develop products that are designed to deter abuse in some route. Those PMRs are more specific to this conversation, where they're expected to provide data to show how that works in the real world after approval, outside the controlled settings of the premarket testing.

I think the example of Opana made it very clear, that product did not have labeling around abuse deterrent; however, that's what the company designed it to do. That was what they intended, their intentions were, or in that direction. And the product was withdrawn from the market not based on anything that was happening in patients taking it legitimately for

pain. It was withdrawn because of the risks relating to abuse. So, I think both of those are within FDA's purview, particularly if that's what we're developing these products to do, the ADF products. We have to look at that as the outcome, and I think that's the outcome we're concerned about here is can we understand better what they do? Can people defeat them? I think when we approve them based on the premarket data, we are approving them as something as a safe and effective alternative for patients to take them in the same fashion that they take the nonabuse-deterrent formulation. So, we expect them to meet their needs. And, as I mentioned with the OxyContin example, if we find a safety issue that is specific to patients, we go down the same pathway we normally do when safety issues are discovered -- weigh that against the benefits and then determine a path forward. Doug, did you want to add anything to that?

DR. THROCKMORTON: You know, I think that's right, Chris, and I agree, there is a clearer signal from the Agency now that we're going to be thinking about the public health impacts of these products.

We've always done that. I mean, there has always been an understanding that these products had both intended uses, safety and effectiveness, and that there were the unintended consequences of their misuse or abuse. And that was included into the regulatory decision-making in a less formal way than I think we're going to do it going forward. You can look at Palladone, you could look at other places where clearly we've taken into account the things that -- abuse and misuse and tried to make decisions accordingly.

Without any question, as I listened to the discussion about what population to study here, it seems to me we're sort of focusing around power. One way to think about this is empowered to detect a difference. So, the notion of using a population that's misusing, that's admitting that they've misused these, seems a little attractive to me because it identifies a high-risk population that may be more likely, more, let's call it sensitive, for a better word, to interventions, like abuse-deterrent formulations. It's a population that will give you more power to detect a difference with a smaller

population provided you believe that the answer you get there can then be translated back to that larger patient population that Sid and Judy I think are both saying. It is the ultimate thing we want to understand.

You could take it the next step. You could use populations of recently incarcerated individuals we know who are at extremely high risk of abuse and misuse and relapse. That might give you another kind of estimate, if you wanted to. But which population to study I think can be severed from which population we're interested in, and I think about which populations to study mostly in terms of our ability to get an answer that we can interpret.

DR. GOLDIE: Dr. Compton, please?

DR. COMPTON: It's a very interesting discussion about whether the population of interest are the patients to whom the medications are prescribed or the broader social network around those folks that may be misusing these. I certainly would encourage you to focus primarily on the broader network that is misusing these drugs. I think the patient population is such a

low base rate for direct -- you know, that pathway you described I think is pretty rare and it's going to be hard to follow, and it will take you 10 years to go all the way down that pathway, and it will just be a handful of people. We have other studies to get at that in a general sense, and I don't think the ADFs are going to make much difference in that long-term pathway.

On the other hand, studying this in a high-risk group could be very fruitful, and I think Dr. Degenhardt's example is a terrific example. I will say that there are US investigators who do just as good a job with their follow-ups. There are certainly investigators like Chris Scott and Mike Dennis in Chicago and Illinois, who have both done it in their own studies and taught many others how to achieve more than 90% follow-up rates routinely in very large samples of drug users. The Washington University group under Linda Cotler and previously Lee Robbins did this historically for decades. And so it's not unheard of. It's very different than sort of the national probability samples, because it does require intense

personalized follow-up. You essentially don't lose the folks; that's how you keep them for 90-some percent, and you make it attractive for them to participate, both in terms of incentives and by making it a pleasant experience for them. So, there are ways to achieve those rates that are essential for the quality of the science for questions that you want answered. But I would focus mostly on the high priority, high-risk populations.

DR. GOLDIE: Dr. Winterstein followed by Dr. Shoben, please.

DR. WINTERSTEIN: This is a great meeting for my question. We started the discussion asking what do you mean with effectiveness, and I was looking back at the first slide that Dr. Meyer showed, and they have actually surprised me, because the outcomes that she showed was the intended or unintended route of use. But then the next one was development of dependence and development of substance use disorder. And that surprised me, because basically the idea would be does an abuse-deterrent formulation decrease the risk for needing more drug and developing subsequent substance

use disorder? And that's a claim I haven't heard before. It's kind of an intriguing idea. The question would be does restricting access to basically more of those facts or decrease the whole risk of that development. I'm curious what the addiction specialists in this room feel about that. I have never thought about the abuse-deterrent products doing this, because if that were the case, then studying initiators and patients would make a lot of sense, because that would be an additional benefit of these products that we haven't really talked about.

DR. MEYER: So, maybe I'll clarify how I got there, and it goes back to your -- Dr. Compton's comment that this is a pathway, but it's probably a pathway that takes a really long time and a very small number of people, right? There's the typical trajectory, there is probably the other one, so this is probably just like one pathway and I was just kind of following it to the end of what that pathway would be.

DR. WINTERSTEIN: Well, but those trajectories can go fairly fast. They don't take necessarily a long time to have somebody who is initiating an opioid

becoming a chronic user and subsequently having substance abuse disorder. That's not necessarily fast, but it's very different saying that a product deters abuse via a non-oral route versus a product prevents development of needing more drug faster. That's the distinction that I think is important to think about, and if the latter is the case, then studying the trajectories of early initiators would make a lot of sense, right? Because that would be a completely different pathway. I mean, in the discussion that we have is we either have patients who already have substance abuse disorder and need more than they get prescribed and start to look at alternative routes to get there. But the other path that you were lining out here essentially, maybe inadvertently, is a different one. It is we don't even allow them to getting more and therefore we basically protect them from getting substance abuse disorder. I don't know whether that's true or not, but that's kind of what we have here, and I think that's the discussion of looking at patients versus -- patients who have chronic opioid needs and pain versus patients who are substance -- who have been

diagnosed with substance abuse disorder.

DR. CRANE: This is Elizabeth Crane. I'm just going to add or are they switched to something else?

DR. SHOBEN: This is Abby Shoben. I really this question is sort of the question that we've been dancing around for the past two days in a sense of, like, who are we really trying to protect with these abuse-deterrent formulations? And I've always sort of thought of them as being sort of a population level kind of intervention that, like, if you sort of could do the randomized trial, it would be randomizing one unit to -- sort of one geographic unit to saying you guys are going to get all of this abuse-deterrent formulation, and a different geographic unit would -- you would just get sort of the control that doesn't have these ADF properties. And then do you see reductions in the rates of abuse by the nasal and intravenous route, assuming that's what the product was intended for. And then I've sort of thought about them as sort of, like, kind of like a vaccine in a sense, like you're protecting both the person who is getting it, the patient specifically, but also all of those

people around them. How you actually study that in practice is an interesting question, but I think that it's -- I've always thought of them as being sort of a more population level intervention and we therefore need to think about how to study that and not just the individual person with a prescription.

DR. GOLDIE: Dr. Schnoll and then Capt. Jones, please.

DR. SCHNOLL: Sid Schnoll. You know, I think we have to begin to put this into the context of what is happening now. If this was seven or eight years ago, I think we would see a lot more people who were abusing prescription opioids. But it's changed, and now we're seeing more illicit heroin, illicit fentanyl, and to some extent this may in fact be because of the introduction of these products. I think some people at the FDA remember when you first brought up the REMS for the ER/LA opioids. I asked a very simple question: Would you consider a benefit of this REMS to be an increase in heroin abuse? And, of course, the FDA said no, but in fact anybody who has worked in substance abuse for any length of time knows that people are

going to go to the easiest product that they can get and use. And when you put an impediment in front of them, whether it's an ADF, whether it's a PDMP that's cutting down on doctor shopping, or something else, they're just going to change to what's easier to get. And it's happening. So, we're sort of chasing the last problem, to some extent. And last night I was thinking about some things and it's sort of like the Crosby, Stills and Nash song, "When you can't be with the one you love, you love the one you're with." And, you know, so people are going to use what's there, what's available.

So, we've got a new situation now, and we have to look at how can we test these products in this new situation? And there are people who are attempting to abuse these ADFs, but that's a shrinking population, and it may not be as easy as we once thought. So, we've got to really think that maybe what we've done has been pretty effective.

DR. GOLDIE: I'm going to give Capt. Jones the last word on question 1 before we move on to question No. 2.

CAPT. JONES: I was just going to add that even looking at people who are receiving prescriptions, I think you can cut out a really large group of people from the start who get a single prescription. If you look at 60 or 70 million unique individuals getting an opioid prescription in the past year, a large majority of those people get one and are done. And I don't know that that's worth the resources that you could get down to the people who are getting multiple prescriptions as a way to follow.

And I also think there has been a huge amount of research in the last couple of years to understand other contributing factors to risk. And if you're looking at a cohort study, you can also identify, even if they don't have a diagnosis, would be sort of dependence and other mental health conditions and other history of substance abuse. You know, different types of things that could help hone in on the population of patients that you're interested in, in addition to looking at a high priority group of people who are already diagnosed with abuse or dependence.

DR. THROCKMORTON: Chris, this is Doug.

That's really helpful. So, quick estimate. Which would be a better way to enrich the population? Use a population that admits to misusing or choose a population, let's say, over 100-morphine equivalence per day, or some other measure of large chronic opioid use, as far as identifying a population you'd be able to test most efficiently?

CAPT. JONES: I mean, I think the people who are addicted are going to be your most innovative folks to try and figure out how do we defeat these products?

MS. BOSE: Can I add something to that? I think using the NSDUH data, in as much as we can't go into the specifics, when you start looking at the population of people who did say they misused in the past year, and then you start cross-tabbing between reasons for misuse. So, I used all the -- feeling pain relief, and then to get high, or all of those other things. And then you also look at the way in which they misuse, so I used it for longer versus for the feeling it caused also. And then you cross-tab it with the sources of the drugs. You really can start to break down profiles of users. And based on those

profiles, it might help you to identify who you want to target. So, for example -- and the other variable is frequency of use.

So, there's a number of broad measures that kind of start painting a broad picture of some of these users. And you will see that, let's see, people who use -- misused it for the purpose of pain relief still continue to have a doctor as their source of the prescriptions compared to people who said that their reasons for use were non-pain relief.

So, I think -- and kind of going back to the earlier conversation earlier during the day, while the national data don't do what you need to do in terms of specific formulas or specific substances, it does at a nationally representative level give you a picture of some -- and it misses out on, again, your prison population, your homeless population, your in-residential treatment population. So, it doesn't cover everybody, but it kind of does start out with the different profiles and maybe help target who you want to see.

DR. THROCKMORTON: I'll just add that on a lot

of those things we have a paper coming out that details many of those things.

DR. MEYER: I think we're going to have to move on. I know you can catch me at lunch and then feel free to submit materials to the docket, and if it -- and we've kind of covered some of -- like the last question already, so if we'll have time we can come back to it.

So, the second question is basically the question I had about confounders. Like, can you help us try and figure out which confounders are the most important? And I guess it depends on the outcome, but if you could comment on both of those things, all of the above, that would be great. We can start with Dr. Dasgupta.

DR. DASGUPTA: Thanks. I was actually raising my hand for this question. So, I think we've talked about polypharmacy on and off, but I think that is one of the more central factors in looking at an individual over time. Especially for low volume ADFs, there is going to be very, very, very few people who are using who only have access to one ADF. And how you control

for that, how you adjust for that in crossover designs, incident user designs, there is a lot of ways to think about it. But I think at the fundamental level your every inference you make from longitudinal individual data is going to be for anything other than overdose mortality, pretty much, you know, is going to be a time-varying exposure. It's going to be something that has changed over time in an individual, especially once you get into addiction or injection or progression or downward spiral, any of these concepts. So, I don't really have a solution, but I think in terms of figuring out what to make of a regulatory submission I think knowing that there is going to be no clean answer, this is something that we should just kind of acknowledge upfront.

DR. MEYER: Okay, real quick. I just want to tell people that we had intended to combine question 2 and question 3. Yeah, because question 3 was this question about characteristics of the comparators, which kind of also answers question 2. So, if you want to comment on either right now, that would be very helpful. Thank you. And we have a queue.

DR. KREBS: Hi. Erin Krebs. And I keep going back to patients, chronic pain patient-prescribed opioids, because that's the population I know. I will say in response to the question about where is the money, where are you more likely to find the people? I don't think this is where you're more likely to find the people, but since it is what I know, that's what I'll talk about. And in terms of the confounders and the comparators, I think if we're talking about patients with chronic, pain-prescribed opioids, the critical thing to keep in mind in that, in general, studies of any risk mitigation strategy find that risk mitigation strategies are associated with high risk for the addiction abuse outcome because prescribers are targeting people with those risk mitigation strategies. They're not applied randomly in the population unless there is some other reason why they would be, or a prescriber only prescribes that particular -- you know, always uses that risk mitigation strategy. But, you know, like frequent drug testing is associated with illicit drug use, not because it causes it, but because prescribers are suspicious it might be going on, so

they look for it. And I think that's a big issue here, if you're comparing an abuse-deterrent formulation, especially if it's a higher tier product, compared with something that is more available, that there is a reason it got prescribed.

DR. GOLDIE: Dr. Green, followed by Dr. Scharman, please.

DR. GREEN: So, I'm still struggling a little bit with the outcomes being measured, and if we think of the ones, abuse, misuse, addiction, overdose and death that we've talked about for a couple of days now, we haven't had the discussion that addiction is not related to one specific product. I think that's the outcome I struggle with the most in terms of assessing a specific product. Overdose and death are events that you can, you know, you can relate more specifically to a product, but I think addiction is the most troubling.

And then when you think about a longitudinal or following a patient, you have to think of ethical considerations, too. So, you get information and you see a patient that is starting to tamper or starting to misuse or abuse the product and are you going to

intervene or not? I mean, this is a discussion for IRBs in these studies, but can you ethically let this patient continue down whatever pathway it is? And so if abuse, misuse are in your primary outcomes and you can stop there and ethically manage the study, I think that's fine, but then to sit back and watch and see who goes on to addiction, overdose and death might be a little more challenging to do. So, that's a comment about following patients over time.

DR. GOLDIE: Dr. Scharman, please.

DR. SCHARMAN: I think in speaking to the question of confounders, I think one of the biggest ones is confounders in trying to determine our denominator in population. I don't think we understand enough about why one specific population in a state has a higher risk of abuse than another county. We have counties that have similar rural populations, degrees of homelessness, degrees of joblessness, and they are high-risk counties. And then we have counties with those same demographics and they're not. Some are opioid abusers, some are synthetic cannabinoid abusers and why? And so until I think we get a better handle

on what makes certain populations more at risk than others, I think it's going to be hard to set our studies so that we have equivalent populations.

So, with the Opana outbreak, why that particular county in that state? Because other counties that meet those same demographics, what happened there? And so I think confounders in populations are something to consider until we really understand why some counties are more abuse-prone than other counties.

DR. GOLDIE: Dr. Lo Re, please, followed by Dr. Brooks.

DR. LO RE: I think from the, just the confounders from the provider level, I think it would be important to collect what was the indication for the opioid prescription and what was the reason that the provider selected that formulation. Whether it was just a formulary issue, was this an issue of they had concerns for -- the person has a history of abuse or dependence. I think from the patient level it would be interesting to know the adherence to the opioid, socioeconomic status, psychiatric disease. We talked

about polypharmacy, but perhaps some individual drugs for particular interactions, chronic liver disease.

And then just to get at, since, as I was hearing through the conversation there were some interest in knowing whether an ADF was more likely being insufflated or injected. I wonder, too, if as other outcomes you could think of sort of infectious outcomes of injection, such as endocarditis or skin and soft tissue infections to evaluate as outcomes as well. And there are certain ways to algorithmize those over time.

DR. GOLDIE: Dr. Brooks will conclude the discussion on question 2 and 3, before we move on to 4. So, Dr. Brooks, please?

DR. BROOKS: While I can't summarize the extensive discussion, but I did want to respond to Dr. Scharman's comment very quickly to remind folks that in the Indiana event, it wasn't an outbreak of opioid abuse. That is occurring everywhere. It was an outbreak of HIV infection that was caused by aspects of the particular opioid that led to people injecting with extremely high frequency, so that when that virus was

introduced into the population, it spread very quickly.

We've done -- for those who are interested, we've spent a lot of time at our agency thinking about how to look forward to where there may be other jurisdictions set up for experiencing the same problem. But the problem we're interested in is not where there necessarily is opioid abuse occurring through -- by injection or inhalation, but, rather, where just injection drug use in general is occurring. It could be from heroin or methamphetamine or any other problem. I will say that one of the values of outbreaks, and if you were to do -- is that they're often sentinel events, so that if a system were set up looking for evidence of misuse, that is, abuse of a deterrent formulation in a way that it was deterred not to be used, so injecting a deterrent formulation. A surveillance system of people who are engaging in the behavior and then turn out to be using the abuse-deterrent formulation, that could be a sensitive -- you could pick up that event. A system like that might sensitize you to detect it. It may not detect an outbreak, but it might detect the event.

DR. LEE: Okay. We're going to move on to the next question, so let's discuss which study designs may be most useful for future studies of the effectiveness and safety of ADF opioids. And Tamra went over some examples of cohort studies, prospective, retrospective, historical, and then there is a case control example, and we are interested in hearing some other possibly novel designs. And although it's not listed, maybe if you are studying longitudinal, if you want to conduct a longitudinal study within the limited budget, then maybe a case cohort study would be an option, too, for those who are familiar with the design. And then when you are considering the study design, please weigh in the resource, intensity and time into the consideration.

DR. DEGENHARDT: Louisa Degenhardt. Just in reply, I guess, to Dr. Brooks, but it actually addresses this question. When we designed the study to look at the introduction of reformulated OxyContin, we've actually got several major components of the study, and the prospective cohort is one of them. But what we've also been able to do is leverage off exactly

the surveillance mechanism that you're proposing, which we conduct every year in all capital cities of Australia, where we interview people who inject drugs regularly blind to what drug they are injecting. And what we're monitoring is which drugs are being injected or snorted or swallowed or otherwise abusing. And the intention, because we're sampling people the same way every year, is that we can detect exactly those things. And that can be done with any new opioid. So in fact we regularly introduce new modules when new prescription medications are introduced into the market, including reformulated OxyContin, but also others with the idea of exactly detecting those changes.

DR. BROOKS: I just have a technical question, which is how do you account for different sampling between your cross-sectional surveys? Is there any method that you use to -- and what I'm getting at is in cross-sectional surveys, it's very hard statistically to argue the trend, to do a trend analysis. But you can sometimes infer the direction something is going if the populations were sampled appropriately and

appropriately similarly.

DR. DEGENHARDT: So, we use the same sampling frame every year, so we go to the same places, we've got the same criteria, literally the same sites. So, all of that is kept as standardized across time as possible.

DR. LEE: Dr. Dasgupta?

DR. DASGUPTA: It seems like there are lots of -- it seems like we all have a particular one, two or three data sources that we inherently trust, and that constellation of data sources is different for each person sitting around the table. And some people place more weight on ethnography or claims, whatever it is. At the end of the day, I mean, if you have to make -- if there has to be a study or a short set of concise studies that make -- that, you know, collective prove a point about safety or effectiveness, it's not -- I don't know how -- without kind of explicit guidance or direction from the Agency, I don't know how to navigate that kind of cognitive bias that each of us carries without kind of explicit, you know, saying, like, these are the -- this is the collection of sources. And I've

noticed in the more recent public discussions from the Agency that there is kind of, here is the primary set -- here are the primary sources and here's kind of supportive sources, and kind of that kind of a description of how to do the ADF evaluations. And so I think we talk about the study designs, talk about data sources, but at the end of the day we're kind of left with this individual cognitive bias of what we think is the best source individually, and I don't really know how to get over that.

DR. GOLDIE: Dr. Ciccarone and then Dr. Lo Re, please?

DR. CICCARONE: Dan Ciccarone. I'm going to bring up my cognitive and other bias, which is toward a qualitative research or ethnography. As a number of people have brought up, most recently I think Sid, the ideas that we're shifting from this general population problem to a more focused problem. We should assume that the ADFs work, right? There is evidence already that they work. Opana was the exception; it wasn't a very good ADF. And so moving toward more focused or targeted studies is imperative, as Dr. Throckmorton

brought up. There is an issue of power now, so we need to increase our sensitivity as the ADFs work. And here's where the advantage of sort of outbreak investigations or targeted studies come in.

Where surveys can tell us the bigger questions of who and when, the qualitative research is going to get us into the how, and that's important in terms of routes and other risk behaviors, and the why -- what's the intent that the users are trying to achieve? Samples may be convenient, but we're going to use that to our advantage. Again, the Scott County example combining survey methodology with ethnography, the sum was greater than the parts. And, of course, all of this fits into a mosaic. You know, the idea is that it's not ethnography or a targeted study all by itself; it fits into these large population studies. In fact, large population studies may tell us where the hot spots are, tell us where to focus our reference. It does exist, samples exist between the general population survey level and the treatment population level in people that have already identified themselves, or others have identified them as addicted

or dependent. These folks are sort of in the middle.

It will help us understand, you know, qualitative and ethnographic research, the confounders, the effect modifiers, which are really key to the last set of questions here. They will help us understand plausibility, right? So, if we're getting into causality, we need to understand the linkages between what we're seeing in the epidemiological data and the social and behavioral plausibility that helps us get to causality. Helps us understand context of abuse, of course. It will also help us understand the issue of polypharmacy, right, as a key thing. I know this historically, we've been talking about polypharmacy for multiple decades now. It's become -- it's been highlighted again now, and we need to understand how people are mixing drugs, and particularly the substitutions. So, I'm in heroin, I want to know which one of these ADFs is going to replace heroin. Hydromorphone, good replacement for heroin, so we need to be particularly careful on the ADFs for oxymorphone.

I'll wrap up soon. I just want to say that, again, surveys can identify the hot spots and then we

can go in with outbreak investigation kind of, or RAPID ethnographies to kind of figure out. And one way in which a survey or outcomes can help us is looking for, as Dr. Lo Re brought up, skin and soft tissue infections, blood-borne viruses, overdose. If there is an outbreak of those, then we can sort of focus on, well, what's going on with this outbreak of abscess or endocarditis, that kind of thing.

We used to have a number of ethnographers in the field, and having a panel survey of ethnographers periodically tell us what's going on in your location. I know NDEWS is trying to replicate this with their sentinel folks, so working with the NDEWS folks I think would be helpful. But I do miss the old CEWG, the Community of Epidemiological Working Group, which had sentinel ethnographers that we can chat with and find out what's going on in various cities. So, I think as we get to questions that we can't quite get answers to, we have more why questions, it does tell us that we need to be spending a little bit more money on ethnography.

DR. GOLDIE: Dr. Lo Re?

DR. LO RE: Yeah, I'm just going to follow up on something that Dr. Dasgupta had mentioned about the different data sources. I would just use caution that the existing data sources, the designs that are employed really should be driven by the questions that are being answered and that are being sought. So, I think certainly for safety, potentially electronic health records would be an option. But I think given the inherent limitations that we've all heard about the existing surveys, the challenges in actually ascertaining misuse and abuse in claims, EHR, that the prospective cohorts and prospective cohort designs of varying populations certainly might be the best option, which is why I think we're all moving in this direction.

DR. GOLDIE: Captain, did you have a comment?

CAPT. JONES: Thanks. Capt. Jones. Not being as enmeshed in the field of opioid abuse, I'm trying to make analogies to general medication safety and effectiveness research. And so I'm wondering what really is different about the safety of these ADFs as opposed to other drugs, if our main concern is safety

among those who are taking them or for whom they're prescribed. And I'm not quite sure what the safety differences are. Most of the adverse events that we find from other drugs we find through things like volunteer reporting, MedWatch. Most outbreaks are reported not so much from surveys and research, at least the surveys that are described here, but either comprehensive public health surveillance by health departments, that's like everybody everywhere for all lab reports of a bacterial infection or whatnot, or, again, by the astute clinician reporting something. So, for safety I'm not quite sure what is different for the safety of these products than other drugs.

Now, of course, if we're talking about immunization effects or effects in like other folks and effects among people for whom the drug is not prescribed, well, then that's a whole other discussion. But, again, if our focus is on looking at the safety of these products for whom they're prescribed, I don't know what is qualitatively different in the products.

DR. STAFFA: This is Judy Staffa. I'll take a stab at that. I think because we're introducing

excipients into products that patients who are taking them for pain don't need, I think we're being very vigilant about making sure we understand. And as these formulations get more innovative, we may be seeing excipients where there is not as much experience. And I think there is -- again, there is testing that goes on in the premarket just like with every other oral product, but I think that's why we're sensitive to that, and that's why we want to pay attention to that. Because we did -- I don't know that we expected to see what we saw with patients having difficulty swallowing. I mean, it doesn't seem like rocket science in hindsight, but I don't know that we were anticipating that, and so, yeah, our usual systems can help. But remember one of the reasons we developed the sentinel initiative is there is a whole lot of drug safety issues that are not going to be reported through spontaneous reports. And so if you think about it that way, it could be other things that we just want to understand better and know about, particularly with the non-API part of these products, I think. Does anybody from FDA want to add anything to that?

DR. THROCKMORTON: Well, I guess, Dan, I think you're talking about ascertainment, maybe, aren't you, which is how the adverse events would be detected. I mean, the source is different. I think Judy is exactly right. We focus our premarket testing, at least currently, on the intended routes. Sometimes we've had to expand that now, obviously, but the ascertainment is not fundamentally different. I think that's what you're saying, isn't it?

DR. CICCARONE: Yes, and then we think about, well, if we're worried about the excipients, then the adverse events either have to be incredibly rare or, I'm sorry. So, we turn to things like sentinel, or we have to do things like cardiovascular outcome studies when these things are either rare or they're so common and we're looking for marginal differences. And I don't know if that's truly what we are worried about here, either those marginal differences or those things that are so rare that we need to -- because if we think it's so rare that we need something like a sentinel, I mean, prescribing use isn't high enough to detect it in something like that anyway.

DR. LEVENSON: This is Mark Levenson. I think you raised a good point, and that point was raised as well yesterday, that this is just another safety issue. But I could say why we may have looked at this differently. Typically, a drug company is not seeking a claim in safety, and in this case we are encouraging companies to seek disclaim -- I mean, this is something that FDA would like to encourage, and with the claim, with an actual claim it gives them an incentive to develop these. So, if somebody wants to make a claim and if they need more rigorous information than typically collected in safety. Then there is also the aspect that we're also trying to protect the population, which you mentioned as well, which is a little different.

DR. GOLDIE: Dr. Unick, I'm going to give you an opportunity to comment and then we're going to move on to question No. 5.

DR. UNICK: Just to answer this question, I think that if we want to have a clear idea of what's going on in populations of folks that are using these substances outside of medical supervision, we have to

engage them. And when we do them successfully, we do them carefully and we build relationships, and we have long-term relationships with folks, and we don't just run out because we think there's a problem. That's fine for a sentinel event, where an HIV outbreak occurs. But if we want to know what's going to happen with future products, we have to develop relationships now and build those relationships over time so that you have the trust of individuals.

This is not a -- you know, for a lot of these folks they haven't had good experiences with institutions or with -- you know, Baltimore Hopkins certainly has a questionable reputation among a lot of folks, but Hopkins still has a very good study with the ALIVE study, where they've developed these long-term relationships. And so you can then leverage this information to figure out safety or what emerging issues are. So, I just want to encourage thinking ahead of time rather than just reacting to events.

DR. LEE: Okay. This is our last question before our lunch break. Let's discuss the feasibility and importance of assessing unintended secondary

consequences of ADF opioids, such as shifting abuse to other opioids, including heroin and such.

DR. MEYER: So, we've already covered this a little bit, if you want to add additional comments, go ahead, please.

MS. CASSIDY: Hi, Theresa Cassidy. As I read this question, I just wondered if others were thinking about it the same way that I was. In terms of the importance of assessing unintended consequences of the ADF opioids, I think that we could probably all agree that from a public health perspective in context, like, obviously, this is important to monitor these secular trends and patterns and what might be happening as it relates to, you know, we're in the midst of a prescription drug abuse epidemic, so that is clearly an important aspect of this question. But I think we've also discussed and seen it is feasible to do that with the variety of different data sources, and that we can see some of these patterns and shifts happening. Where I struggled a little bit, and this is relative to the two examples that were here, shifting to abuse of other opioids, including heroin, I so struggled with how that

comes back to the product level versus, like, maybe ADF as a group, and how you relate that back to the success of a particular ADF because that's based on the routes that it was intended to deter. And I think the example that Opana was slightly different, where it was actually related to injection and maybe like injection drug users are sort of a sentinel group and we need to kind of take a look at that. But if we're seeing shifting to, like, you know, fentanyl and other things, absolutely it's an important public health, you know, outcome to watch for a monitor, and sort of see what's happening. And maybe that prompts us to understand where we need to have other types of abuse-deterrent mechanisms to stop those types of abuse, or try to deter that type. But I was just struggling a little bit with this question of how it relates back to the products themselves.

DR. STAFFA: This is Judy Staffa. Maybe I can try to clarify a little bit, again, just from the way I'm struggling with this, is that I don't -- I've heard people voice the opinion that if we do something like have abuse-deterrent formulations, or any other kind of

intervention, and that causes people to shift more to low-cost heroin, have we done something good? And if you go down that pathway -- I don't know the answer to that question; I think it's a real difficult question. But if you go down that pathway, it can almost take you to a pathway that says, well, then we shouldn't do anything, and I don't think that's very wise. But on the other hand, are there ways to understand that knowing that as FDA we don't have much control over Mexican cartels and the availability of low-cost heroin. We understand that that's out there; is there a way to be able to understand that as an outcome or as some part of this picture that wouldn't necessarily mean anything good or bad, but simply be a factual piece of information, which is important to understand. And, you're right, I don't know whether you look at that for ADFs as a whole or whether that is something -- again, we are a little -- after the Opana experience, I think we're trying to make sure we're thinking about this in the broadest possible way. I don't know that any of us really thought that would happen at the very beginning, but as that began to become clear, I think

it's making us want to make sure that we're positioned to understand on intended consequences should we begin to see them again and be able to react quickly. Does that help at all?

DR. GOLDIE: Dr. Schnoll, do you want to respond?

DR. SCHNOLL: Yeah, Sid Schnoll. I think, Judy, you bring up a very important issue. We're looking at a very complex problem when we talk about addiction in general, and people have spent thousands of years trying to address it. And in terms of products with reduced abuse to treat pain, the College on Problems of Drug Dependence has been working on that for almost 90 years now and we haven't done it. There will be adverse consequences, but I don't think the FDA should stop in doing what they're doing in trying to get better products on the market. But what has to be understood is that this problem is not just the purview of FDA, that it's much bigger, and there is only so much that one agency can do to address a major public health problem. And the FDA is trying to do what it can, but it's got to include a much broader societal

approach to this, including other agencies, as I mentioned yesterday, trying to get meetings of these other agencies on a regular basis to try to address this.

So, we've seen, as I mentioned earlier, this shift. Was this shift to heroin and fentanyl analogues due to the ADFs? Maybe to some extent, but we have the PBMPs, we have education, we have the CDC guidelines. I mean, we could talk about all these things as being part of it. Can we measure what degree each of these was part of that? I'm not sure we can get to that point, but that's why I get back to what I said very early. FDA should be looking at what its products can and cannot do, and not go beyond that and try to say that it's going to solve a much larger problem. It would be like saying, you know, statins are supposed to get people to stop eating bacon, or anti-diabetes problems -- products are supposed to get people to stop eating chocolate cake. It's not going to happen.

Define what you can do and go after that, and measure that. Don't try to measure things that you can't control. I think that's, to me, the bottom line

on this. And if you try to do too much, it ain't going to work.

DR. GOLDIE: Dr. Crane, followed by Dr. Ciccarone.

DR. CRANE: Yeah, I totally agree with Dr. Schnoll. I mean, this opioid problem didn't come out of nowhere. People are calling it epidemic, but it's been growing. You know, we started tracking it in 2002, and it was probably there before then. But the core people working on it were not the people that had the ear of the policymakers, too. So, I think, yeah, I think doing all of this deterrence without funding effective treatment is a big part of it, and that's not FDA's responsibility. But FDA has been very good at working with SAMHSA and other agencies on -- and now there is a big push. So, anyway, that's just my comment.

DR. CICCARONE: Dan Ciccarone. Yeah, so, I'll just state some obvious things in terms of this question about the intertwining of opioids and heroin. We could spend the next two days discussing the trajectories and what caused what, and basically the

answers are unknown. And anyone's hypothesis about this begot that, most of what I've heard, the hypotheses out there, have some degree of truth.

The point moving forward is, is there, since the population has intertwined, the opioids are intertwined, the outcomes are intertwined, is there a potentially substitutable product that we allow through the gate? And that's what we need to -- do we need to screen for? The reason why the ER/LAs were at risk, I'll state the obvious -- high dose in a single pill, crushable, snortable, you know, the alternative route thing that we talked about, chewable. And the abuse-deterrent formulations are trying to address that, so that's the key issue that we're talking about today, but there is still circumventable, right? So, that's what we're looking for. But which is the next one that's going to be figured out, right? There is a hierarchy of opioid out in the world of desirability in terms of euphoria. We've kind of forgotten -- Sid and I were talking about this last night -- we've kind of forgotten what the hierarchy is, but I'll just say the obvious ones. You know, hydromorphone is way more

desirable than hydrocodone. And so which of the more desirable opioids, are their ADF-ness good enough? That would be my --

As a heroin researcher, that's what I want to know is, are those nonsubstitutes? And, yes, the heroin epidemic has a complete life of its own at this point in terms of supplies, adulteration contamination with fentanyl and the like. And that has less and less to do with what we're doing on the prescription side of things in the region that's effective right now.

DR. WINTERSTEIN: I'm not sure I'm a good wrap-up, but I will try. I think this question, in terms of having patients with severe addiction, who are considering moving to heroin, I think the help there is treatment programs and buprenorphine and methadone, not withholding other agents, but to providing something that addresses the problem. Because that's what's needed. And given that reasoning, I don't think that there really are unintended consequences of making the drugs that are approved for the purpose of treating pain to making them harder to abuse, as long as there are alternatives for treatment of substance abuse

disorders available. That's how I'm looking at it. I mean, those medications we are discussing today are supposed to treat pain and not substance abuse disorder. And perhaps therefore the unintended consequences are really not an issue in that context, because this unintended consequence is somebody who has developed substance abuse disorder already and will need something to address that.

DR. SCHARMAN: So, speaking to your question 5, secondary consequences may be more to the acute secondary consequences. I think over time poison center data, part of the National Poison Data System, has been very good at looking at shifts based on availability of consequences. So, for example, when hydrocodone-acetaminophen products went to C2, you immediately saw on our database a huge drop in those exposures. When buprenorphine -- we track this at our center -- when a number of prescribers of buprenorphine went up in our state, our number of pediatric poisonings of buprenorphine tracked that increase. So, we think our database is pretty sensitive to shifting from one drug to another when a certain drug is

restricted. So, I think, you know, we've already talked about it. It's not a perfect database, but it is pretty sensitive to those. Again, as Dr. Boyer mentioned, I think if you wanted to use our database for heroin, that would be a mistake. Hospitals don't call us because they get it all the time and they know to use naloxone. But we do tend to get a really good sentinel source for the bizarre things that drugs do. So, if a particular ADF caused a really nasty effect, if someone tried to manipulate it and inject it, we'd probably be more likely to get that call, because it's an odd route of the drug, they have this weird acute effect, and they might ask -- they might call us first.

So, I think that the poison center world is one place, not the place, but one place to look at for those immediate, unintended, secondary consequences of the ADF. And I think we do get adverse drug reaction questions as well. So, again, we complement MedWatch and some of the other ones. I think all of those reporting systems have their pluses and minuses, but we complement that. And so I think if a patient was prescribed an ADF and all of a sudden we saw this

cluster of patients that are reporting this weird effect, that would be one way that those could be picked up on.

DR. LEE: Okay, thank you for the comment. It is really the time to wrap up this session. We're going to come back at 1:30 for audience participation. Enjoy your lunchtime.

DR. STAFFA: Okay, we're ready to get started again. I know everyone is so excited. Session 7 and 8 are going to be fantastic. But first we're going to finish up session 6 with our audience participation. I'm going to turn it back over to Hana.

DR. LEE: Okay. The rules are the same. If you want to participate in the audience participation, please line up. And green light means you can continue speaking; yellow light means you have a minute left; and then the red light blinking, please stop immediately and return to your seat. Please speak your name and affiliation one more time, please.

DR. COPLAN: Thank you. Paul Coplan from Purdue Pharma and adjunct professor at University of Pennsylvania School of Medicine. Just wanted to

mention that we are doing a cohort study for -- we're doing two cohort studies. One of them is the one that Dr. -- three cohorts. One is that Dr. Levenson mentioned, which is 3033-2, which is on clinicaltrials.gov, which is a claims database. And then we're also doing a cohort study. But for OxyContin, we -- the fourth study involves a retrospective claims database study to look at the incidence of overdose. And I think there are three issues we're working through on those studies and if people had any thoughts on that, we would really appreciate it.

The first one is statistical power. So, we are working in two large insurance claims databases, MarketScan and HealthCore, that involve 140 million lives covered between them. And the power to detect a reduction for OxyContin pre to post is we have 80% power to detect a 30% or 35% decrease. So, 20% decrease we would not be adequately powered. That's just for OxyContin. Then there is a question of the real outcome is difference in difference. Is there a difference in OxyContin relative to the difference for

either morphine or something else? And the difference in difference is interaction effect, which is a very low powered test, so we then have much less power to detect a difference when we start to do interaction tests. So, we are struggling with power.

We are much better powered on the opioid use disorder outcome, because that's about 10 times more common. And we have in fact done a preliminary study, which we published, that shows that while there was an increase in opioid use disorder in most opioids, there was a significant reduction for OxyContin ER after reformulation, about a 20% reduction. That also is a more relevant endpoint for payers, because the opioid use disorders are a chronic condition and costs a lot, so that is much more relevant to payers.

But the other issue is multiple opioids. So, some people would just use one ER opioid alone. But a lot of the patient abuse is that people will use IRs for a long period of time, then the physician will add the ER on top of the IR, keep the IR at the same dose. So, now we have a substantial amount of IR use plus the ER. So, the IR has its own -- contributes its own risk

of overdose that's not going to be affected by an abuse-deterrent formulation. So, one question is, do we use just -- you know, some people like Matthew Miller has just looked at one opioid alone, monotherapy, so that you can tease out just the effect of that opiate. Others have used all opioids, but then you attenuate the effect of any abuse-deterrent formulation by all the other opioids, if there are concomitant opioids that are being used. So, if people have any thoughts on that, that would be very helpful for us. Yeah, I'll leave it at that, thank you.

DR. DEVEAUGH-GEISS: Hi. I'm Angela DeVeaugh-Geiss, also from Purdue Pharma. I just wanted to make a brief comment about comparators. The issue has come up and kind of peppered a number of the discussions, but there doesn't seem to be a direct conversation about that, and I think it's a really important consideration when designing these studies and trying to determine whether there was a change. I think there's different options for how you choose comparators. There can be therapeutic equivalence. So, for example, another ER opioid, if you're comparing

to an ER abuse-deterrent formulation, or abuse equivalence, so things that people are likely to be switching to. So, for example, there's a study that was done that some of you here know more about than I, using the RAPID survey and the SKIP data, looking at what individuals who had been abusing OxyContin are likely to then report abusing afterwards. For example, IR oxycodone single entity. And so it would be very helpful to hear both from the panel and more from the FDA about kind of the intent behind the selection of comparators, which are chosen in part by FDA with some additional input from the sponsors, but to hear what others think as well.

DR. HENNINGFIELD: Good afternoon. I'm Jack Henningfield, Pinney Associates and Johns Hopkins School of Medicine. I have kind of a big picture comment, where this fits. Yesterday, Sid Schnoll mentioned the interagency committee that helped coordinate drug control and communications. It's not clear that we have had such coordination in the last few years, and so it's not surprising that the media often flat-out get things wrong, such as that AD

opioids aren't working because we have increased fentanyl and heroin problems. This meeting has several key agencies together, and I really hope that the conversation among the agencies will continue. I think that's really important. We have to be consistent with surveillance and reporting in the communications. We shouldn't be counting illicit fentanyl, for example, as prescription drugs, or conflating prescribed patients, who are not the main problem, with nonpatients who report using prescription opioids as their first substance of abuse when we don't even know what they were using.

A big issue is how AD opioids fit into opioid abuse and control efforts while addressing under-treated pain. Blunt instrument approaches hurt low income and people in minorities. We know that draconian restrictions on prescribing, one-week prescription limits, overly burdensome prescribing requirements can hurt the people that are hurting the most, and that's a serious problem.

FDA can't wrestle the opioid problems in America by itself, and AD opioids as we've heard over

and over can't do it by themselves. But other interventions, such as treatment on demand, that has to be part of it. We have to make sure that what we're doing here today fits into the big fabric that hopefully is being created.

AD opioids efforts need to be integrated with comprehensive efforts, as NIDA has advocated, and the Addiction Society of Medicine, American Society for Addiction Medicine. We need to know if insurance payers and the VA are paying for products. If the products sit on the shelves, they're not used, they don't help. We need treatment on demand, so when somebody asks for help, they get help, and they're not asked if they have insurance or money, and if so, to wait.

CDC's Top 10 Public Health Advances of the 20th Century provides some models that are worth looking at. They all involve comprehensive efforts, they involve innovations in technologies, education, look at automobile safety, seatbelts, which are now required, improved highways, education, infectious disease control. Again, innovations in medicine,

education, wash your hands, and so forth. You need big, comprehensive, coordinated efforts to make big changes.

Finally, I hope that you will have input into the report being developed by the White House Commission on the Opioid Crisis. I think it's really important to emphasize that AD opioids and other innovations in pain medicines are part of the solution, but that we need surveillance to guide interventions and track consequences of our efforts intended and not intended, as well as the surprise that history shows should be no surprise. Thank you for your efforts.

DR. LEVENSON: So, thank you. We're going to start our seventh session, and Cindy Kornegay will provide the introduction and presentation.

SESSION 7: LEVERAGING OTHER DATA: LINKING AND BENCHMARKING

DR. KORNEGAY: Good afternoon. Before we begin discussing the session, I'm going to provide a very brief overview of leveraging, linking and other benchmarks that can be used to investigate ADF opioids.

So, in the last day and a half or so we've

discussed many aspects of ADF opioid investigations including product identification, population sampling, the study designs, and various other aspects in the implementation and design of these types of investigations.

So, when we started to talk about linking or leveraging or benchmarking, or any of those terms, applying that to the data resources, we came up with about three reasons, three big reasons why it would be desirable to do so. And the first reason would be to provide additional statistical power. Often, even in very large single data resources, the number of individuals who are possibly exposed or definitely have the outcome can be very low, so this could be a good way to increase the study size. To provide additional risk factors and/or confounders, since there is a wide variety of risk factors that need to be considered for certain conditions, and a single data resources, particularly if it's a clinical data resource, might not have adequate data collection in all of those areas. And, finally, to provide additional context to enhance generalizability. And I'm going to give brief

examples for all of these.

So, when it comes to providing additional statistical power, there are large collections of healthcare data, and they do have a large number of individuals, but many of these individuals are at very low risk of abuse-related overdose or death. These individuals generally are stable enough to hold a job and, quite honestly, pay for health insurance, which means they are probably not spending all their time on drug-seeking or drug-using behaviors. And even some of the organizations that don't require this kind of stability, like the VA, have in recent years increasingly stringent restrictions on opioid dispensing.

Now, there are many, many smaller practices that include pain management and addiction management, and these would have a wider variety of patients of interest to us for ADF opioid studies. But they are less accessible for a variety of reasons, which can include technical limitations, lack of resources, fear of exploitation or litigation. Or possibly it's just the easiest way for the practice to ensure patient

privacy and compliance with the legal landscapes that can be very different between states.

As an example of using several data -- linking together data resources to achieve and create study size, it's a study that's a key part of the extended release and long-acting postmarketing requirements, or ER/LA PMRs that FDA has asked industry to conduct.

The primary study is a prospective cohort study that will use data from several different resources. And the purpose of collecting, getting patients from these different resources is to increase and enhance the target population of individuals who are on long-term therapy for chronic pain, and also to ensure adequate participation of individuals who are at high, medium or low risk for the outcomes of interest.

Now, the second category of additional risk factors. Well, prescription drug abuse has a variety of risk factors and outcomes that are not always predictable, and they are not always included in clinically-based data resources. And so one of the things that we periodically explore is if it's possible to link or leverage clinical and nonclinical data

resources kind of in tandem. And an example of this is an FDA pilot project that we are conducting. Well, actually, the state of Connecticut is conducting it and has involved the FDA, and this is going to link exposure, treatment, outcome and mortality data within the state of Connecticut. This is a proof-of-concept project, and the goal of this project is to determine if an opioid which is dispensed to a patient is also the opioid that is involved in an overdose or other outcome of interest.

And also to just emphasize the need for additional risk factors, this is one of the slides that Dr. Meyer had put up in her presentation. And I'm not going to go through it, just like she didn't, but just to emphasize that the relationship between the risk factors and both the exposure and the outcome are very complex. For example, information on social networks and pain and socioeconomic status are unlikely to be included all in a single data resource, which kind of emphasizes the need to pull several of them together.

Now, the third is to provide -- the third reason, which is to enhance generalizability, and this

would be really to be able to benchmark a small or large convenient sample to a nationally representative estimate. Now, we do recognize that we would need to find data resources that would have -- the national base data resources that would have this capability. And we're not quite sure of what that data resource would be. I mean, the census data is kind of obvious, but we're not sure if it would have all the important variables, if the demographic variables that the census data do have are what's needed to help achieve this type of estimation.

And as an example, which is kind of outside of the abuse realm and also a proto example, several years ago FDA had access to outcome-based evaluation -- outcome-based data -- or, I'm sorry -- hospital-based data for a very large convenient sample. So, we had inpatient drug utilization data, and we wanted to know if we could create national projections of that inpatient drug utilization data from this very large convenient sample to the entire country. And so what we did was we compared the information in the sample to the National Hospital Discharge Survey, and I'm sure

I'm dating myself, since that survey has been out of commission for a little while. And while the National Hospital Discharge Survey had demographics and procedures and discharges, it did not have drug use data. However, we were able to look at the information that was similar between the two data resources, and that facilitated our understanding of how representative this convenient sample was and where it could and could not be used to protect information nationally. And so although this did not require the actual linkage of data at that time, it was actually a way to leverage one data resource to the other.

And so, finally, I do want to acknowledge that we are fully and extremely aware that there are many, many challenges to doing this. It's difficult to do it when you're just looking at different types of clinical information, and so trying to link from clinical to nonclinical would be even tougher. So, some of the challenges might be technical, identifying patients, or identifying time periods when the databases were consistent. The update frequency of a linkage would also be an issue. Is this a one-time thing or is this

going to be something done periodically, and if so, how would it account for changes in the database?

Confidentiality we think would be a huge factor. Not every organization allows patients with substance use disorder diagnoses to be identified, and you would also be dealing with increasingly small sample sizes. And contractual restrictions which might have been in place before linking or leveraging or benchmarking was even considered. As an example, in the early days, some of the PDMPs were not allowed to link to either commercial entities or across state lines. And so with that, I'm going to turn it over to my colleague, Kunthel, who is going to tee up the discussion question. Thank you.

DR. BY: Thank you, Cindy. Originally, we had three questions for this session, and we've decided that there is a sense of overlap so that we could combine them into just a single question. And the question is not on the slide, so I'll just --

DR. STAFFA: And it's a really, really big question.

DR. BY: So, I'll just read it to you. So, I

guess, the long question in some sense betrays our lack of experience in this space, this space of linking. So, I'd like to apologize in advance if it seems vague. So, here's the question. We'd like to discuss linkages, leveraging, benchmarking, or additional data resources and opportunities that could enhance ADF opioid studies. Please describe the resources, what additional information or advantages it would provide in terms of adding sample size, adding risk factors, and/or enhancing generalizability.

So, in terms of that third one, I was thinking this morning of what Dr. Bose was saying about the NSDUH, when she mentioned that when you're looking at the people that, at least in terms of one year, past year abuse, that you could drill down to specific subpopulations of those people and in some sense looking at the characteristics of those individuals. So, I was thinking back in terms of what we have in terms of poison center data and treatment center data, and asking myself, okay, so you have here these people that are described in NSDUH, even though it's a subpopulation. Can we use that information somehow,

either combining them directly or using the kinds of weights that are available in the NSDUH, and somehow applying those weights to the treatment center people, or the treatment center sample that we have, and in some sense say something broader than just saying, okay, this is what we observed among the people that seek assistance in substance abuse treatment centers. So, I'll start the conversation with that.

MS. BOSE: I might have to defer it or ask a better analyst than I to answer, because I'm not the strongest analyst. But if you're talking about, are we going back to the issue of denominator and exposure, or are you talking about something different?

DR. BY: There -- in the numerator data only, which is the treatment center data --

MS. BOSE: The treatment, right.

DR. BY: -- you just have counts, counts of people who either abuse one product or another product, right? So, in some sense they provide sort of an approximate sort of information about what people are doing. And we want to be able to sort of go beyond that data and say, if you can dig deeper into the

population of people who abuse substance, could we in some sense overcome that sampling issue stuff that I talked about in session 2 yesterday, by taking some of the information in NSDUH and then applying it to the count data somehow, and having it be more generalizable. Not necessarily to the US population or the population of patients, but the population of people who abuse drugs.

MS. BOSE: Because when you first started talking I was thinking about catchment areas and where they were receiving treatment, what are the characteristics of the area they are receiving treatment, assuming we can collapse several years of data, and so there's sample size issues there. But that doesn't exactly sound like what you're talking about. You're almost talking about kind of remediating or, you know, dealing with the fact that some of these are not random samples and can we use random samples -- or known probability samples, too, and I don't know. I don't know what the --

DR. BY: So, can they talk to each other and understand each other.

MS. BOSE: Right, right, right. Local level linking is a little different than borrowing strength from a random sample in order to inform a nonrandom sample, and I'm not sure. I don't have a lot of experience in that domain.

DR. UNICK: So, one thing that's been done in other areas is to leverage existing probability-based samples, replicate their methodology in smaller cohorts that are targeted, and then make inferences using the larger probability samples to have a sense of what the benchmark is. So, people definitely do this, and, for example, the MEPS data site could give you information on how people utilize prescription drugs over time, and then you could target more specific populations that you were interested in, in looking at how those differ from the larger population sample.

DR. STAFFA: And, for the record, that was Dr. Unick.

DR. KORNEGAY: So, to start off -- oh, sorry.

DR. GOLDIE: Dr. DeFrances?

DR. DEFRANCES: I just wanted to talk a little bit about the Hospital Care Survey. I'm not sure

relevant for -- but in the Hospital Care Survey we collect inpatient, emergency department and outpatient visits, and we get all visits. And part of that is we get personally identifiable information -- name, address, social security number. So, we are able to link across settings. We can tell if someone comes back to a sampled hospital for a repeat ED visit or hospitalization. But we can also link to outside data sources, such as the National Death Index. We're doing some work, we got some PCORI funds and actually working on perfecting the algorithm to linking to the National Death Index, which is housed at NCHS. We are also going to be doing another pilot study where we'll be linking to CMS data.

I think in the future, again, once the survey gets up and running, it hopefully will add some value to looking at substance involved ED visits, but I think a real important thing -- and, again, this is something at NCHS we haven't been able to do is we can take visits, but we can also talk now about people, patients, and that's not something we've ever been able to do before. So, I know we've been partnering with

FDA and SAMHSA. Our biggest problem has been hospital recruitment, getting -- it's a voluntary survey, it's getting hospitals, but I see tremendous value, the Hospital Care Survey, to hopefully shed some light on some of the issues we've talked about today, but also as future issues come up. Again, it only deals with hospitals, someone coming to the ED or an inpatient, but still I think hopefully will have tremendous value in the future.

DR. STAFFA: This is Judy Staffa. Can I ask a follow-up question on that? That's very exciting, to be thinking about linking those data to death data and to CMS data. And I just want to throw out the question: Are there any potentials to link those data to PDMP data or to treatment center data, or to kind of broaden that linkage?

DR. DEFRANCES: Again, I think it could be. Right now, when we go to hospitals, we say upfront where we're going to link the data. I think we would have to tell hospitals -- again, it's voluntary, so in our letter we say that we're going to -- we want all your visits and we're going to link to NDI and CMS.

We'd have to work through that, but I think it has the potential. We'd have to tell the hospitals upfront. And then there's the IRB and confidentiality issues, but it could be explored.

DR. GOLDIE: Dr. Dasgupta, please?

DR. DASGUPTA: I saw you mentioned linking to NDI for claims data and such. So, some of my pharmacoepi colleagues at UNC are looking into the quality of the linkage with Truven and other claims datasets to NDI, and it's decent but it's not as good as you'd expect. And so they're working with going a level deeper and looking at social security numbers and trying to get data from -- we are working with the Social Security Administration data to try to get a better -- kind of do a validation study on the NDI linkage in claims data. And we definitely are seeing certain places where things don't match up as well as you would think. And so I think for, as a field we jump into, the NDI linkage with claims data, specifically, I think for these questions of interest, I think there is a little bit more methodological work to be done.

DR. STAFFA: So, this is Judy Staffa again. So, I have a question on that. Because for years we've been linking claims data to NDI for specific study questions. So, are you talking about efforts to link on a specific issue, or are you talking about more of a standing linkage, where that linkage exists and is updated regularly, and then when you have questions, the linkage is already there?

DR. DASGUPTA: So, both. So, it's looking -- so, the original product was looking at it as a global, all-cause mortality linkage, but a subset of the study is looking at it specifically for opioid-related outcomes in opioid patients. So, there's -- the work isn't done yet, but I think it's worth being a little bit cautious on that.

DR. GOLDIE: Dr. Parker?

DR. PARKER: I can speak to the issue since I led the record linkage program at NCHS for about five years, and actually looked at all those NDI linkages, all the ones that met that code in the middle that were ambiguous. I can tell you that if you have good social security numbers, we can probably link that really

well, but if you don't have good social security numbers, it is going to be difficult. And I don't know about all these populations, but you can guess at some of the populations that we don't have good social security numbers for. We also don't necessarily do the best with people who use nicknames. You know, like if you're Jenny all the time but you're Jennifer on your death certificate, you're not going to be -- you know, it will be flagged. And so people who use different names, people who change their names, marriages, divorces, there's all sorts of issues. But we are working on it and, as Carol said, we do have a grant or some money to evaluate those algorithms, and I think we'll be doing that.

More generally I could talk about all the problems with record linkage, since I spent most of my time working on it, but I think I'll talk about some of the advantages.

For your question, at NCHS, what we do is we link all of our surveys that are linkable all together. And so what, for example, we'll be collecting all the HIS data, all the HANES data, some of the hospital

data. And we'll link that all to the CMS data, all at once, all the Medicare data first, because that's easier, all the Medicaid data second. And what that does is it provides a lot of data that is overlapping.

So, we'll get data for the Health Interview Survey from, say, 2010, 2011, 2012, 2013, 2014, 2015, linked to any Medicaid record that's available. And so for someone who is in our survey in 2012, we can have Medicaid data from 2008, or we can have Medicaid data from 2016, depending on the status of the linkage program. And so what that allows for you to do, if you're interested in some of these studies is to say what's the point of time that you're interested in? So, if you're interested in what's going on in Medicaid in, say, 2016, or whatever our latest data year are, maybe it's earlier, you can look at survey data going back. And so some of those survey elements, like education and income and marital status, and things like that, they might be a little bit -- considered more static, but your point of time might be the Medicaid data. Or you could do it differently and say what was going on and who was prescribed something in

2012, and how are they responding on your survey a few years later? And so there are a lot of different study designs that you can use with linked data, and so I would encourage you to think about that.

One of the things that we do at NCHS is that we really like -- and Barry can confirm this -- we really like to have national data to link to the national surveys, because we don't want gaps. So, for example, if you have a health plan that's spotty or not -- doesn't necessarily cover everybody, we probably wouldn't link that. But Medicare, Medicaid we're linking to housing data, programs like that. The SEER data, it's not in all the states, so we can't link to the SEER data. So, when you're talking about some of the other data systems, if you know that -- if it's national, it can be linked to the national surveys. Otherwise, there is just too much unknown. So, I think I'll stop there.

DR. GOLDIE: Dr. Graubard, would you like to respond to that?

DR. GRAUBARD: I won't respond to that part.

DR. GOLDIE: But you did have a comment?

DR. GRAUBARD: Yeah, so, actually, I just wanted to ask Jennifer, what percent are you getting social security numbers for nowadays?

DR. PARKER: Well, that was one of the problems I didn't start with. One of the key things that we need to link is the consent of the survey respondents. And when we were asking nine-digit social security numbers for the Health Interview Survey, the percent of people that was giving us that number went way down. And it doesn't go down randomly; it varies by some of the usual suspects, so you have to really handle that. When we started asking for four-digit social security numbers, it went back up a little bit. I think it's around 70% for the Health Interview Survey. It's a little higher for HANES, but it also is going way down. If -- people that are giving blood tend to give their social security number. People in government programs tend to give the social security number more often than people who don't. I guess they're used to giving the government their social security number. So, there's a lot of things that go into that.

I think Carol's data comes under a different -- comes in a different pathway, and so we don't need individual patient consent to link her data. We also don't -- we haven't in the past needed consent to link to the NDI, although our ERB has changed that policy. So, I think we're going to be only linking people who consent to the NDI now. So, things change.

DR. GRAUBARD: Could you say a little, Jennifer, about the fact that if someone has a dataset and they want to link it to a survey at NCHS, kind of directional aspect of that in terms of who has to give who data here to do the linkage?

DR. PARKER: So, you're just asking me all the problems.

DR. GRAUBARD: Well, it's important because --

DR. PARKER: Yeah, it's very important. So, NCHS data are covered under CIPSEA, as was said, and we don't let our data out. So, all linkages have to be done inside. And so for organizations that have similarly restricted policies, there is just no mechanism to put them together. I mean, we found that with some of the cancer data, where the cancer centers

don't want to give their data up, either. And so just putting -- getting over those hurdles of linkage were difficult. But all data that are linked come to us. And then they don't go out; they stay with us. You can come to us and look at them, but they don't go out. They're available in our research data center. And we do work closely with our collaborators to try to facilitate that, but we care a lot more about the confidentiality for our respondents than we do about any particular research project.

DR. GOLDIE: Dr. DeFrances, you had a comment?

DR. DEFRANCES: No, I was just going to respond that the Hospital Care data, again, we have a waiver of patient informed consent, so we just get -- the hospital is the entity that gives permission, if they give us the PII.

DR. GOLDIE: Dr. Brooks and then --

DR. BROOKS: Judy, I just wanted to clarify, you asked about the PDMP. And as Jennifer was noting, it's not available at the national level yet. It's available right now state-by-state, so you have to make an individual arrangement. CDC has a contract out to

Brandeis to try and create a national set. It's not there yet, it will be one day, and then you'll be able to tie it all together neatly.

DR. STAFFA: Yeah, it's Judy Staffa. And that's one of the data sources in the Connecticut pilot project is their PDMP, but we also bother Brandeis as well. We're in on that one, so we're continuing to watch that grow.

DR. GOLDIE: Speaking of, Dr. Kreiner?

DR. KREINER: Thanks. So, yeah, we're not close -- 12 states at this point. I wanted to talk about a different -- Massachusetts Department of Public Health for the past two years has a pilot data-linking project called Chapter 55, where -- and so this has proceeded in one-year increments based on legislative authorization to do it one year at a time, where PDMP data, all-payer claims data, hospital discharge data, emergency room data, treatment admissions data, death certificate data, some rudimentary criminal justice data are all databases that can be linked at the individual level. And in addition, some community level data, like naloxone distribution and drug seizure

data are available as well. The trick is the research so that the data are linked behind a veil, identify data, and then they are made available to researchers who have applied to do this in a de-identified format. And, of course, all the usual issues with record-linking, data-linking, or any record-linking is an ongoing issue just with PDMP data by itself. And then when you're linking to these other datasets it's compounded. And, of course, there are the usual issues of data quality and all that. But in enables some really innovative research to take place.

The other trick is that the data that you've requested to be linked are linked for one -- for that session. You go to DPH, you sit there at a computer, you work on the data for as long as you can stand to do that, and then once the session ends the data, the linkages go away, so you would need to initiate a second session. So, there are limitations, and I think there may be other states that are looking at this, something similar. And each year with this project they've been able to add additional data and data years. So, the power is increasing, I think.

DR. GOLDIE: Dr. Dasgupta, please?

DR. DASGUPTA: So, having done studies where we use PMP-linked mortality data in a couple of states, I can tell you that the quality of linkage between states is quite variable. Some states do it using portions of names; other states use full names. There is a lot of variability, so trying to get a national picture I think is difficult. There are a handful of states who are already doing that linkage on an ongoing basis -- Utah, for example, and so those are potential sites. But in a recent research effort we were trying to combine as many states as we could into -- we already had linked PMP mortality data and we basically ended up realizing that the linkages and the data quality were so different between states that combining those wasn't going to work right away.

One interesting PMP mortality linkage that goes beyond overdose is Kentucky has just agreed to link all-cause mortality with their PMP, so I think that has the potential of -- and doing it on a monthly basis prospectively. So, that may be a new data source for this that is more exciting.

DR. KORNEGAY: So, one of the other -- oh, sorry, Dr. Kreiner?

DR. KREINER: I just -- just as long as there was a lull, I want to make a small comment about VA patients. So, as you may know, for the past few years the VA, National VHA has been in the process of submitting, having state submissions from their facilities to state PDMPs. We've been able to look at that data in several states and in particular Kentucky, we found that about a third of the patients who pay for prescriptions by VA are obtaining prescriptions paid for by other payment sources. And in particular, when cash is one of those other payment sources, they are much higher risk scores for those patients compared to the VA, the patients that use VA payment only. So, even with the limitations of PDMP data, it can give insight into specific populations.

DR. KORNEGAY: So, in addition to the state level linkages, yesterday I believe it was Dr. Unick who talked about using dark web information, and Dr. Boyer talked about using urine testing, and understanding that there is no way that we could do

this nationally or even regionally. Would there be a state or a local way to kind of operationalize using that data in some way that would assist in investigating ADF opioids? Like, how could we possibly, for example, link urine testing data, which is really nonclinical because it's often collected through law enforcement and other places, to maybe treatment center data, or something where we don't necessarily know who it is, where anonymity or confidentiality is maintained, but we have the benefit of that information.

DR. GOLDIE: Dr. Dasgupta, please?

DR. DASGUPTA: So, we've been -- I can speak to the Dark Web data. So, we've been -- in my previous job we had been monitoring dark web sales and posts for about seven years, and it was very useful in capturing things like we were detecting the fentanyl analogues back in 2010 well before it became kind of an established problem in the US. There's a lot of -- the data are very, very difficult to use. As has been mentioned, markets go blink and out of existence on a regular basis. The formats of the posts are not

standardized between marketplaces and the -- certain marketplaces cater to certain populations either by language or a geographic location, or by the types of things that they allow to be posted. There's a lot of nuance there. So, I think Dark Web data, and we've looked at ADF kind of impressions, right?

So, the market listing itself is interesting. But what's usually more revealing are the comments of, just like on any kind of e-commerce site, where you have user feedback, right, for people who have purchased it, you have the same thing. And you get a lot of people saying, like, oh, this isn't really that -- you know, this ADF isn't that good; you should try this one instead, or whatever. So, it's qualitative. It's hard to do in a systematic kind of quantified manner. You can probably do it -- there's a few aggregators of listings, and those folks are -- at least one of them is research-friendly, so you can do things with that, with kind of scrapes. But at the end of the day I think it's not going to be a quantitative data source, but it can provide some listing, but it's not easy.

DR. GOLDIE: Dr. Crane?

DR. CRANE: Another potential source that is really taking a long time to get it going, the health information exchanges, which there may be other people who know more about them, but electronic exchange of information of patients. It could be done at the state level. I think it's probably related to the Affordable Care Act, or CMS, but I think the idea is that a physician can login and get access to that patient's information from their primary provider, from other sources.

Now, there are some state-run ones, like I think Indiana supposedly somebody said everybody in Indiana is in theirs. There are others that are more local, and there are some that are just being done by nongovernmental. Maryland's is called CRISP. So, that might be something to look at for the future. John? John Squeet (ph), okay.

DR. GOLDIE: Dr. Kreiner?

DR. KREINER: This again is about PDMPs, but there are a couple of PDMPs that are integrated in HIEs, so Maryland's is one where PDMP records are

automatically linked with the claims data in HIE, the patient record in HIE. Nebraska is another one. And there are at least a couple of PDMPs that are now starting to incorporate other data fields with the PDMP data. So, Wisconsin, for example, is including information reported by law enforcement about any arrest, drug-related arrests for suspected misuse/abuse, goes into the patient record that the physician can access. And there are related fields. I think at least one other state is looking at adding overdose information, both fatal and nonfatal.

DR. STAFFA: This is Judy. Can I ask one follow-up question on that? Since we're talking about PDMPs, and Cindy had mentioned that at the beginning, many of the PDMPs were only state-specific and they couldn't talk to each other, even if they wanted to. How much has that changed? Is there a lot of interaction? We're hearing that, but we don't really have a sense of how widespread that is.

DR. KREINER: So, the vast majority of states can exchange data with other states, PDMPs. What that means is a provider in one state can query their PDMP

on a patient and be able to access data theoretically on that patient from some number of other states that they can specify. It does not mean that the bulk data is being linked with across state lines.

DR. GOLDIE: Dr. Crane?

DR. CRANE: I was just going to mention that we're developing an algorithm for natural language programming to find drug-related visits, and we're looking for a data source, and the Maryland HIE hasn't worked out. But it wouldn't be to produce estimates, but it would be to give us information to help us develop our tool.

DR. KORNEGAY: Dr. Green?

DR. GREEN: I wanted to move into the benchmarking. I don't know if that's --

DR. KORNEGAY: Sure.

DR. GREEN: -- where you -- it's part of the discussion or not. I couldn't remember the merged question.

DR. KORNEGAY: Whichever you want to discuss is fine.

DR. GREEN: And this came up earlier when we

were talking about the online surveys and benchmarking. But I think there is opportunity in that space to benchmark things like online surveys with NSDUH or other nationally representative surveys that may not get to the granularity that we want with product specificity. So, if we can, say, for instance, show that NMURx is an appropriate sample or an adequate image or picture for the national representativeness as benchmarked by, say, the NSDUH survey, then we can utilize the product specificity and some of the other trends over time. You know, these surveys are probably going to be a little bit more flexible and quicker to change.

And then to the timeliness, too, because, basically, as mentioned with the Mantra (ph) survey, have 30,000 respondents in a few weeks and really be ready to lock your data in a matter of months, not waiting much longer than that. I see them as very complementary. Not that one is better than the other, but I think there's work to be done in that area.

And then the same -- I've already spoken with you about -- in understanding the treatment centers and

what they actually do represent in relation to the world of treatment centers using NSSATS information or other ways to understand what that looks like.

And then for the benchmarking, if you can establish what that sample looks like, can we then do more, you know, better national estimates or find ways to model that out to a larger population?

And then I think for poison centers there's all kinds of debate of, if poison centers are a good indicator of death or not, and if that outcome is -- if poison center data is an appropriate measure for death. And the work we've done in comparing the death reported to poison centers and then what's in NDI shows that the trends over time can definitely be said there is high correlation. Of course, they are drastically under-reported, obviously. I think it's somewhere between, depending on the molecule, between 5% and 8% of the deaths that are reported to NDI, actually, are in the poison center database. But further exploring that maybe by state to see if there is differential reporting between ER and IR products to better understand what does get reported to poison centers for

deaths, and then maybe use that also as a model to build out what that actually represents. Because, again, it's a little more timely product specificity and the value that you get from some of the programs, even though you know that it's under-represented.

DR. GOLDIE: Dr. Scharman?

DR. SCHARMAN: Yes, I am speaking to the question of potential data sources. So, I kind of mentioned this before but not in this context. The dynamic of where people receiving treatment has changed, so I've traditionally looked at treatment centers, emergency departments, physician offices, and now this widely expanding use of lay public naloxone changes where these people that are abusing drugs are seeking care. So, whether there are risk reduction programs that have expanded beyond needle exchange, which gives us some piece of information, to they also dispense naloxone. More and more pharmacies are now dispensing naloxone, and so those potential chains, CVS, Walgreens, have huge databases. And looking at the -- you know, maybe linking that data to buyers in naloxone and people getting other prescriptions might

be a potential database. I'm sure there's lots of dirty data and confounders, but it's a population I think we have to look for that we haven't had before, and we need to look at, is there a way to survey those users to collect data from those sources? Because those are people actually at high risk for drug abuse, because they're getting naloxone. Not all, because some people are buying to have in use for other people who are addicted, of course.

But I know in West Virginia, in order to track dispensing naloxone, they're using the Prescription Drug Monitoring Program, for better or for worse, as a way to track those. So, again, I think we need to be forward-looking as that program expands across the country as potential data sources to find people who are high-risk users of opioids, or family members of high-risk users who are buying it. And the local health department risk reduction programs are going to pick up the people that aren't buying it themselves, and the pharmacies are going to pick up the people that have insurance or money to buy it. So, by combining those two, you might get a broader range.

DR. GOLDIE: Dr. Lo Re?

DR. LO RE: Yeah, just a question. I heard that you were linking in Connecticut, maybe I misheard, the Prescription Drug Monitoring Program with some other data; is that right?

DR. KORNEGAY: Yeah, it's a pilot program that's actually very similar to the one that Dr. Kreiner described in Massachusetts of basically taking all the information that's available at the state level. So, those who get insurance through the state treatment PDMP data, mortality data, emergency department data, kind of whatever they can get in there and link together.

DR. LO RE: Could either of you just comment how good in regards to your first sub-bullet, misuse and abuse definitions? Do we have any sense on the validity of misuse and abuse definitions in the PDMP data at this point?

DR. KORNEGAY: Dr. Kreiner?

DR. KREINER: So, there is a literature that has linked prescription histories to overdose deaths, sometimes other kinds of outcomes, like in claims data

diagnosis of abuse, but there is no -- there is not a widely accepted threshold, if you want, or defined measure. There are so-called risk indicators, and you can do sensitivity analyses around that. So, average daily dosage of opioids, use of multiple prescribers and multiple pharmacies overlapping opioid prescriptions, overlapping opioid and benzodiazepine prescriptions, things like that. But when those measures have been studied in literature, there are different thresholds that have been used that have been found to be associated with the kinds of outcomes of interest. So, at this point they are indicators. That some are at a higher threshold is probably extremely likely, but there hasn't been an extensive sensitivity analysis around that, that I know of.

DR. STAFFA: This is Judy Staffa. Actually, one of the 11 ER/LA PMRs for those manufacturers is around validating doctor shopping and pharmacy shopping definitions, hoping that we would then have definitions that would be able to be used more broadly. But I don't think those studies are done yet.

DR. KORNEGAY: No, they aren't. And to

specifically respond to the question about Connecticut, this is just in the beginning stages, so I don't know if it's even gotten to that stage of design yet.

DR. LO RE: So, I'm just asking because -- and this is one of the key outcomes that you had proposed in the five originally. Dr. Levenson, I think in your roadmap this morning you had mentioned that there were some efforts at trying to develop algorithms for validation. I don't know if those are ongoing and there aren't any data at this point, but it would seem to be potentially somewhat challenging. So, I was just thinking if we're talking about linking PDMP with potentially EHR or claims data in the future, that's going to be valuable if you can identify misuse and abuse. And I'm looking at a website from the CDC for prescription drug monitoring program, and it says that they are designed to monitor information for suspected abuse or diversion. So, that's why I was just asking, do you actually have some evidence on a patient-by-patient level that there is abuse diversion, then it would be valuable if those were validated. But I'm just asking because I don't use these data regularly.

DR. GOLDIE: Dr. Kreiner?

DR. KREINER: So, such risk indicators actually have more than one purpose, so researchers might wish them to be as accurate as possible for the purpose of PDMPs to alert prescribers, for example, when their patients hit one of these risk thresholds. They are much more willing to accept, you know, false positives in the interest of trying to prevent further issues. So, that's why PDMPs use these thresholds to trigger alerts, for example. But they're less interested in whether they are perfectly accurate or not, as long as there aren't very many false negatives.

DR. LO RE: Just to push, do you think, then, to go back to some of the earlier questions about other ways to improve data, do you think that maybe that somehow using the Prescription Drug Monitoring Programs, leveraging those existing could potentially improve ascertainment of misuse and abuse, that would be feasible?

DR. KREINER: Well, so my opinion is yes, and it's a moving target, so as people shift into other opioids, as people recognize that PDMPs are monitoring

certain thresholds and may try to game that a little bit. So, yes, it can be refined but it's likely to change. There is already a lot of variability across the country and it's likely to change over time as well.

DR. KORNEGAY: Are there any others who care to make a comment or propose a new data resource for us to go off and explore? Okay, then I think the next is the audience participation.

DR. BY: Yes.

DR. LEVENSON: Cindy, if I can interrupt here before we start this. Ms. Bose, when you opened the session by saying there were two purposes we might want to make use of NSDUH, but let's explore the ways we didn't discuss in this session. You said possibly for catchment areas. Could you elaborate on that?

MS. BOSE: So, I haven't done a lot of work in that area, but people have looked at, they've looked at data from the NSSATS, which is a universe survey of all substance abuse treatment facilities in the nation. And they may have used TEDS data as well, which are both admission and in some cases for some states

person-level admission and discharge data for the treatment of substance abuse disorders. And those records identify the top three substances for which a person received treatment. And they've -- I think people have tried to look at population characteristics surrounding those treatment areas and make different assumptions and conclusions based on that. So, that's one of the areas where they've done it.

Similarly, I'm not entirely sure how it translates, but people have looked at distance, veterans and distance to VA facilities and the nature of the population in local areas. So, that was what I first had thought of before I was trying to actually parse out what you had asked me.

DR. LEVENSON: And do you feel the national surveys could be useful in this regard?

MS. BOSE: I think the national surveys are characterized by their limitation in this regard, because -- several different things. Sample size is the first one, and even if we were to pool, for example, on many measures not only do I have consistency between 2002 to 2014, but I also have other

measures that you can compare. But the moment we start going into the local areas, we just have limitations. Like, if you look at county level estimates, there is maybe, I don't know, 100 counties for which we can make estimates. And the other issue is, if we're trying to study something that is rapidly evolving and changing, then the cumulation of years is really counterproductive to what we're trying to do. So, I think that the national studies, unfortunately --

And some of the things I was mulling about is that we do small area estimation, where we do use the area resource file, and we use private vendor data and come up with estimates. But even there, there are limitations and the areas for which we do come up with estimates are substate and they may or may not be useful. And I was also trying to go back to some of the work that I think the Bureau of Transportation statistics has done, because all transportation is very local as well. So, if you have local area transportation data that's not nationally representative, I'm not completely sure, but I believe they have tried to, again, using that borrowing of

strength concept, they've tried to say, okay, we have a certain limited pool of data; we have certain data about the characteristics of that area; can we borrow strength not from a national dataset, but from other areas with similar characteristics? But that's very much model defined. It really depends on the quality of your model and the input data that can go into it. So, I'm not sure if what they've tried to do in the field of transportation can be transported to this domain, either.

DR. GOLDIE: Dr. Boyer?

DR. BOYER: Yeah, so keeping in mind that weird is my specialty, I don't know exactly how to intercalate this into like PDMPs and nationwide datasets. But are you guys familiar with the MIT garbage project, or trash project? There are certain parallels here with that thing. The trash project is based on the following premise: We know an awful lot about supply chains, but we don't know -- well, we know hardly anything about what happens after something leaves a supply chain. Like, we don't know how garbage is removed, in other words. I mean, we know where we

pick up garbage and where we take it, but how it goes from point of sale into a home to a landfill isn't nearly as defined as when it comes from manufacturer's position into a home. So, they essentially radiolabeled 500 people's trash -- I think it was in Seattle, and then put RFID readers, but it would probably be Bluetooth now, around the city at strategic locations, and that gave a sense of how flow was moving around the city.

So, if you had a geographically constrained location, you know where something should be going, you can identify all the locations where it should be; then you can identify by subtraction all the places where it shouldn't go at the same time. I don't know how that fits into, like, how do you split out, you know, like taking a pill and injecting it versus snorting it? You know, like when you should be adjusting it, but I'm just throwing it out there as another interesting way of getting data on use and movement of items that may be of some benefit to you.

What we've done in the naloxone space is we've actually put Bluetooth emitters on RFI -- sorry, on

naloxone syringes that we've distributed from our emergency department, so we can figure out whether or not they actually enter production -- or enter the community at all. Notably, one individual received naloxone, he left it, he went home with it, he came back two hours, and he got it after an opioid overdose. He came back two hours later with another opioid overdose, because he took his naloxone syringe home, put it in the top drawer of his nightstand, and then proceeded to overdose the second time. So, I can kind of apply it to drugs -- you can apply it to drug misuse, but how to put it in terms of tampering with the medication, I haven't quite gotten my head around that just yet.

DR. STAFFA: Any further thoughts on that? Anybody want to get up in the stratosphere with Dr. Boyer? Dr. Compton?

DR. COMPTON: I'm almost always willing to enter the weird zone with Dr. Boyer. I think that -- it reminds me of a comment I made yesterday that, are we following the pills instead of the people, because that's really what we're talking about. And I don't

know a way to solve this issue.

And Ed is reminding us of one potential way, but are there ways, instead of thinking about surveying groups of individuals, figure out where the pills are going and then track a certain number of them. Especially if you can figure out who the high risk people that they're going to and then track those particular pills, not the people. But you got a prescription for this particular ADF; what did you do with that? Where did it go? Where is it now? Who used it? How big is it?

I mean, I am coming back to a little more of the ethnographic work that I think could be another really important data source. I mean, we haven't talked as much about Internet chats and discussion groups that came up a few times, and I wasn't here for all the discussion, so maybe it came up other places. But I think that's -- it won't give you the overall rates at all, but it will tell you where to look, and it will give you some hypothesis-generating information. And, also, if somebody has figured out how to bust open the abuse-deterrent formulation, it

may show you that, which is really important, irrespective of how many people are doing it.

DR. CICCARONE: This is Dr. Ciccarone. Since we're in the stratosphere, happy to hang out with you all there. Testing paraphernalia. You got, you know, discarded syringes and other paraphernalia that is in the waste stream somewhere that can be captured and tested.

DR. GOLDIE: Dr. Green?

DR. GREEN: Well, I want on the crazy train. What about -- and for all the way smarter R&D people, is it possible that you could have an actual platform that sends a Bluetooth signal when it became disengaged? Or do you actually have a pill, so if it is able to be crushed or dissolved or if that basically explodes or comes apart, then that signal is sent out and then you do have rates and you do have, 100% theoretically catchments of every pill that goes out of the manufacturer.

DR. GOLDIE: Dr. Boyer?

DR. BOYER: I mean, it's conceivable. We've built mockups of naloxone syringes that send out a 3G

signal whenever the plunger is depressed, so you can tell the time and geolocate precisely where it's being administered. So, it's doable.

DR. STAFFA: This is Judy. I just want to throw in a little reality check back down here on the ground. I'm trying to imagine -- I'm still stuck on the exploding pill and what a patient is going to do with that when they're trying to just take it?

DR. BROOKS: They'll let you know when they've taken it.

DR. GREEN: The pill doesn't actually explode, just when the platform disengages. So, when they defeat the mechanism, a signal is sent to say, hey, it's kind of like, you know, success. You know, just something that gives you an indication. Because what we're trying to measure again, right, is the tampering. Like the abuse-deterrent formulation we are trying to measure, you know, is that preventing inhalation, injection, chewing? And the only way you can do those things is if you can disintegrate the pill to some extent. So, if you can get to that actual action, yeah, yeah.

DR. GOLDIE: Excuse me. Dr. McClure wants to contribute, Dr. Unick wants to contribute, and then Dr. Kreiner? Oh, boy, did you open something up.

DR. MCCLURE: Okay, we'll get up in the ionosphere here from the analytical toxicologist perspective. This isn't something that's available now, but there could be prodrug formulations of some of these drugs when we look at them. And from a prescription drug-monitoring program, if you take it as an enteric compound, it's going to metabolize, on release to drug you'll get the desired effect. But if it's not metabolized you may still have the prodrug that's there.

From a prescription drug monitoring program perspective, you could monitor your patients, you could look and see prodrug versus not prodrug. So, you could help differentiate some of those individuals that are supposed to be using drugs in the appropriate manner.

Yeah, those are some of the things that are out there. We talked about the markers that are available. Well, that would show that the drug has been used. But I think when we're talking about

something common, though, with the drugs, enteric, it means it's going to be digested, it's going to be absorbed. So, maybe prodrug is something to look at with the pharma groups.

DR. GOLDIE: Dr. Unick?

DR. UNICK: A little less mission impossible would be going to actual users and asking them about their preferences for abuse deterrents. So, conjoint analysis or willingness to pay kinds of analyses could ask about different mechanisms of abuse deterrents and see what folks that are wanting to defeat these mechanisms prefer. And that will give you an indicator of where you shouldn't go, or at least what they believe are easier to defeat mechanisms. Because you really do have a pool of people that are actively seeking to defeat your deterrents, and if you talk to them they might be willing to tell you how and why and what their preferences are.

DR. GOLDIE: Dr. Kreiner and then Dr. Crane.

DR. KREINER: So, I was going to suggest a more indirect approach, but should the ADF be defeated -- well, let me back -- so, you can use PDMP data to

construct patient-prescriber networks, and you can identify high-risk patients and the prescribers who prescribe to them. At least in certain geographic areas, such networks look to be fairly stable over a period of time.

So, should an ADF be defeated, I would expect that drug to diffuse into such networks. And so rather than trying to pick up an increase in prescriptions across the whole state, you'd have localized samples that you'd be looking at diffusion into. I think that would be a pretty good signal that ADF had been defeated.

DR. GOLDIE: Dr. Crane and then Dr. Brooks.

DR. CRANE: I'm interested in how the information about how to defeat it is disseminated outside the local area. Is this something people put on YouTube?

DR. UNICK: Yeah, you can search the web for this. They'll tell you how to microwave them and then boil them and microwave them again and boil them again. There will be recipes.

DR. GOLDIE: Just go ahead.

DR. MCCLURE: Yeah. While one of the presentations was going on earlier I was looking on the Net, and there are some actually very creative and actual factual ways that you could do solvent extraction of the drugs in the appropriate alkaline-acidic environment, as well as what I would look at as even aqueous extractions using things like lemon juice that are out there with and without the use of microwaves. And it's detailed very quickly, very easily how it's done.

DR. CRANE: We have white hat hackers you could extend that to, you know, this issue, also.

DR. THROCKMORTON: Yeah, just to be clear, we do this. We have formulations chemists that spend their time doing this to products when they're submitted to us. So, yeah, you're absolutely right, it is an essential part of the assessment.

DR. GOLDIE: Dr. Brooks and then Ms. Cassidy.

DR. BROOKS: Yeah, I was just going to mention -- this is Dr. Brooks -- with regard to Dr. Kreiner's point, there are in the past, and you mentioned this too, I think, Dan, that folks have used returned

syringes to monitor for the presence of hepatitis C, hepatitis B and HIV. And if there were a way to detect the ADF chemical signature that was different from others, you could use batches of syringes that are brought back and set up a monitoring program that way. You get into a difficulty handling sharps, but I think that could be overcome.

MS. CASSIDY: This is Theresa Cassidy. I just wanted to respond to Dr. Crane's question about -- and some of the discussion about whether, you know, this information exists about how to extract, manipulate. I mean, looking at Internet discussions and drug discussion forums, we've been doing that for a number of years, and we can look at the different types of recipes. And you're exactly right, there's all kinds of different types of extraction mechanisms. You can start to quantify them and look at those patterns and look at how they relate to specific products. So, that is part of the measures and metrics that we can think about using so that information is out there and does exist, pretty specific.

DR. BY: Okay. I think it's time for the

audience participation now. So, you know the rules. Follow the traffic signal. As you come up, state your name and your affiliation.

DR. STAFFA: Does that mean Dr. Coplan has left the building?

DR. BY: I guess we can go on a 15-minute break. Thank you.

SESSION 8: NEXT STEPS

DR. LEVENSON: Okay. We're starting our last session of the day and the last session of our two-day workshop. And rather than probe specific issues, we thought we'd go with the big questions, chiefly, how do we fit together some of the ideas, some of the ideas for studies that came up to get sort of the mosaic picture. We recognize going into this that one study was not going to be sufficient. We have multiple questions, multiple populations, different endpoints we look at. So, it's sort of going to be a mosaic approach. So, I'd like the panel's thoughts on what -- what are the components of that mosaic together that would kind of get at the questions we're interested in. And we'll probe certain ideas as go along. So, what

combination of studies are needed to address the questions we're interested in?

MS. BOSE: Before we talk about that, the thing that I kept struggling with is prioritization. And, again, coming from that bigger question of all the things we want to understand, including some very, very specifics about the trajectory of how you take -- you know, quite possibly starting from pain management and then going all the way into addiction or not, or substitution. And these are such huge ideas that I kept thinking if I -- fortunately, I don't have to -- but if I were have to beat this into shape, where would I start? And I keep starting from how do I take these picture concepts and break it down into specific research questions that I'm trying to answer, and then further down and further down. And then kind of say, okay, I'm going to take these and prioritize them, and also categorize them as, relatively speaking, low-hanging fruit and complex. And then kind of maybe using that as a starting, two-dimensional grid, identify what is super hard but we can't let go because that's part of our fundamental mission. And then

what's interesting and a low-hanging fruit, and there is value in it, obviously, and we can get to it. So, I think almost before even answering that it might help to break it down.

DR. GOLDIE: Dr. Crane -- oh, I'm sorry.

DR. STAFFA: Hold on. Well, I'm going to try to take a shot at that. So, I want you to think about the fact that you are the scientists at the pharmaceutical companies who are receiving this request from FDA. You have an abuse-deterrent formulation that deters abuse, or you believe it does based on the premarket data to certain routes -- that may be snorting, that may be injecting. And you are tasked with trying to demonstrate that it actually does that in the real world, and you know that you can't go to any one particular place and you can't do any one particular study. I think we've beaten that to death. So, you need to have a mosaic approach, and we've talked about a whole lot of different designs and we've talked about a whole lot of different ways of pros and cons of different approaches to doing that. So, you have to put together a mosaic of how you're going to

approach this. What studies are you going to undertake? Now, I'm not imagining you have, you know, endless budget and endless time; it has to be done in a reasonable amount of time, and you have to pick the designs and the fit together that you think is going to absolutely give us the most information possible. So, if you're the scientist sitting in that seat and you have to do this, let's base it on science, but a little bit of reality in there, because we can't do everything we just talked about, especially not the stuff Dr. Boyer was talking about, right? So, we have to think about -- sorry, just kidding. So, we have to think about what do we think is the best foot forward? And, again, that may be very different for many of you, and I'm going to ask you to even go further, to take in mind something Dr. Dasgupta said is, a lot of folks are coming from a background where if I have a hammer, this problem must be a nail, right? So, let's try to step outside of that and really think about what's actually going to solve this problem here. What kind of combination of, I don't know, three, four, however many studies. We don't set a number, we just say it's a

mosaic and these studies should somehow, at least conceptually, fit together and inform each other, as we've kind of alluded to, but now what does that package look like to you?

DR. LEVENSON: This is Mark Levenson again. And, again, we're interested in both kind of short-term solutions, things that we can implement relatively soon, as well as long-term solutions. So, the low-hanging fruit and also maybe what would be more ideal in a longer-term picture.

DR. GOLDIE: Dr. Crane?

DR. CRANE: You're not going to like this, Judy, but I think -- I mean, I think the issue with the mosaic is, yes, yeah, you have to bring together different sources of information with different -- so different. But they're going do what they think you guys will accept. So, I mean, I think it's partly like what -- if you have any standards -- I didn't mean that. I mean --

DR. STAFFA: Just a few. Just a few.

DR. CRANE: At the (unknown) Research, several of us think that it's really valuable, but it's not

necessarily a large-scale thing. You know, people have been doing applied anthropology for a long time. So, thinking about what standards you want to apply to the proposed research to say, yeah, this is okay, you know, with web research -- I mean, Jonaki, I think, talked about methodology. So, I think for some of these areas there needs to be a bit more firmed up like the strengths and limitations of approach, so you know what you're getting and how to interpret it. But I think, yeah, and government isn't always very good with things like the particular, I mean, ethnographic stuff. It gets funded, but that's not, you know, one of the big priorities. And I think that that's -- you're starting -- this is a good starting point, but I think it's, you know, it's going to -- discussion, but this is going to have to continue.

And you may want to -- I'm sorry. I don't know if you could let a pharmaceutical company do a pilot or proposal about what they're thinking they would kind of try this out without really committing to it, so you could evaluate it. I think this is called the agile approach, you know. You know, kind of work

on an ongoing basis so you don't wait until they kind of put something together and come to you and you're like, no, no, this is not what we want. But kind of have a more interactive way of doing it.

DR. GOLDIE: Capt. Budnitz, did you have a comment?

CAPT. BUDNITZ: Capt. Budnitz. So, I was going to try to put on a kind of actual hat and I'm in a drug company and I'm trying to get an answer that is maybe -- maybe this is something like I'll start with the equivalent of a Phase 1 study, something that's cheap, easy, fast, and can show some evidence of safety or effectiveness. And I think I would, you know, pick up on John's suggestion, where if you look at a group of folks that are already IV drug users and you try to identify if your abuse-deterrent product is being used in that group. And you couple that with, you know, market data that says we have a lot of sales in this local region, so it's something that you could realistically do quickly. You could -- it's relatively inexpensive. It's kind of like a Phase 1 type study, just to show that you don't have anything unexpected.

Obviously, if you then see a lot of IV drug users using it, well, that's obviously a problematic kind of signal and you have to do something, but that might be like a first step. So, I'll just start off the discussion there.

DR. GOLDIE: Dr. Schnoll?

DR. SCHNOLL: Sid Schnoll. I brought this up at the very beginning yesterday, and we have to be clear on what problem we're trying to solve here. And I'm not sure we can do good studies without defining the problem, at least that I was taught, the scientific method, to find the problem and then you move forward. If the problem is to see if people are trying to somehow get past the ADF of this product, I think there are some ways that you can do that. If the problem is going to be, gosh, we've got this huge opioid problem in this country; we need to solve it. Forget it. I mean, we're not going to do that, and to try to even get close to that is not going to be something that's doable or any company is going to try to undertake.

DR. STAFFA: So, it's the former.

DR. SCHNOLL: Okay, thank you.

DR. STAFFA: What's in the mosaic?

DR. SCHNOLL: All right. Just wanted to get that clarification from you. So, I think at that point you can do some of the larger studies, like RADARS, like the Inflexxion NAVIPPRO system, which pick up things. You can look at some of the geographic things that are happening. We know that RADARS looks at things in the three-digit zip code, so you can pick things up and look at with some ethnographic studies of what's going on, if you're seeing a problem in one of those three-digit zip codes. You couple that with a cohort study looking at what's going on with the population that has been prescribed the drug. And you look at this over time, maybe two, three years, to see if you're picking anything up. And I think Dan's comment about maybe you want to concentrate on areas where you have a large number of prescribers, which you can do. You can pick that up. That gives you something to look at, and you can see, is there concordance with what you're picking up, say, with these larger studies with what you're seeing in your cohort study? I think that's something that's doable,

that a company can think about, but I caution that the politicians and the public is looking for something bigger. So, FDA is going to have to change the narrative as to where they are. FDA is not going to be able to solve the opioid epidemic, and somehow that message is going to have to get out there.

Last night I was thinking about this, and those of you who work in addiction, and I'm a recovering academic, so I want to read to you the Serenity Prayer, which opens up most 12-step meetings. And it says, "God grant me the serenity to accept the things I cannot change, the courage to change the things I can, and the wisdom to know the difference." I think if we think about that and where we are, what we can do and what we can't do, I think that's extremely important in not trying to do everything.

And I also want to sort of, when people are talking about big data, I have a favored quote from Albert Einstein, who said, "Not everything that counts can be counted, and not everything that can be counted counts." And so we have to be very careful as we move forward, define the problem, develop studies that

address learning about that problem, and not try to do too much with loads of data that will only confuse us.

DR. GOLDIE: Dr. Lo Re?

DR. LO RE: I think in addition to the cohort studies that Dr. Schnoll had suggested and that Dr. Budnitz, the studies that Dr. Budnitz had suggested, I think certainly some low-hanging fruit might be to do some retrospective studies to look at proxies for misuse and abuse, like looking at infectious outcomes that I had mentioned before, HIV, hepatitis C, endocarditis.

I guess one of the things I would just say that in all of the studies that we -- the proposals that we had talked about, since one of the key objectives is to compare the incidents of use and misuse and in essence to determine whether the abuse-deterrent formulations are effective, I felt like we didn't spend as much time actually discussing the appropriate and valid ways to actually ascertain the outcome of use and misuse in various modalities. We sort of tiptoed around it, but my sense was that it's going to be somewhat challenging in existing data

sources to do that. And that really questioning patients sort of longitudinally using qualitative methods or ethnographic, however we want to, you know, that probably will be the most optimal way.

But I think giving consideration -- because you mentioned that use and abuse as two of the key of the five main endpoints. And I felt like those are somewhat certainly challenging to determine in retrospective cohort, case control -- you know, retrospective claims or EHR data. But giving really strong consideration to that in addition in the mosaic approach using the retrospective studies to look at various proxies for use and misuse, and then also doing these cohort studies.

DR. GOLDIE: Dr. Krebs?

DR. KREBS: Well, as someone who does prospective patient reported outcomes, comparative effectiveness type research, and also someone who is not often accused of being overly sympathetic to industry, I think it would be sort of cruel to ask them to do prospective cohort studies among patients prescribed these drugs, looking at these outcomes,

which I think are vanish -- I think these behaviors are vanishingly rare in the population, overall population of patients prescribed these drugs. New starts of long-acting opioids are not going to become more common as guidelines or disseminated into practice, and I think it would be an exercise in futility for all if that was the recommendation that came out of this.

So, if there are cohort studies, let them be in populations that are substance-abusing populations, not new patient prescription cohorts. You know, I wouldn't propose such a study because I wouldn't believe that I could recruit those people, retain them, or get enough outcomes to say anything about the relationship between the exposure and the outcome. So, that would be my comment there.

I think if there is going to be large studies of patients, they should be looking for signals of things like, for example, inappropriate prescriber behavior that might be associated with prescribers not understanding the purpose of abuse-deterrent formulations. So, perhaps looser prescribing because we're over-confident that these drugs are safe and

can't be abused and can't lead to addiction. You know, something that could be done with large databases, that kind of stuff. But if you're going to do prospective cohort studies, I wouldn't start with the prescribed pain patient population.

DR. GOLDIE: Dr. Winterstein?

DR. WINTERSTEIN: I'd like to defend Dr. Lo Re's idea. I actually came to the very similar conclusion, but just to respond to the most recent comment on this, I think that study that Dr. Lo Re was describing would lend itself to a case-control study and really old-fashioned case-controlled study, if you will. It could be nested in an administrative claims cohort so that there is better prescription data available.

But technically, if there were outcomes on overdose and infection, that could easily become a case control study that would be current that could ascertain prior exposure information on illicit as well as prescribed opioids, which I think would be very intriguing. It would overcome the sample size constraints and the issue with long-term follow-up of

patients and so on. I don't think that would be a cohort design.

The other thing why I like what Dr. Lo Re said, I've been actually wrestling with this since I arrived yesterday. You know, we always struggle with the use of surrogate outcomes in evaluating effectiveness and safety, and to me abuse-deterrent is somewhat of a surrogate outcome. What we really ultimately want to do is we want to improve public health. And what links to abuse deterrent is we don't want people to use opioid in a non-oral fashion, and why would we not want to do this? What is bad about IV use? There is a higher infection risk and there is a higher overdose risk.

So, at the end of the day, ultimately, these are the outcomes we are really interested in, right? Because otherwise the whole idea of abuse deterrents would really not be important. So, I would not describe those outcomes, and I think those outcomes in a case control design could be targeted and there would be -- there would be, I think, very feasible ways of ascertaining exposure information. Again, it's an old-

fashioned case control study pre-claims data that I'm talking about, but it might be a good way to get to them.

DR. GOLDIE: Dr. McClure and then Dr. Dasgupta.

DR. MCCLURE: Yeah, coupling both concepts I think there. When you look at the substance use disorder population that is out there, these are individuals who are already seeking support and behavioral change. If you look at that population that's there and you query them in a study, so that you look for either past or concurrent abuse-deterrent medication utilization on there, and then within that population of that subset, then you look for did they convert to IV or nasal insufflation use of those abuse-deterrent medications? The next step then would be to query, if they did, what was the outcome of that? Did they continue to use the abuse-deterrent medications in a manner that they were able to subvert them, or did they choose other drugs, or did they do some combination? Out of that you could also determine what the identification was for those abuse-deterrent

medications. You're going to have the power of the numbers to at least be able to get information along that line to see, is it being converted to nasal insufflation or intravenous use? And then you could look at that as applying it to then the general population. You could see, does that apply to the numbers that you don't know at that point for general population?

Looking at a situation where you have pharmacotherapy, though, and you have a healthcare provider and they're giving them abuse-deterrent medications, if you're trying to query that group and look for it, you're going to see very low power in terms of your statistical numbers on there. And if you do come across those settings, I think that if when you see intravenous use or nasal insufflation, that's a trigger at that point for that healthcare provider to then transfer that patient into a substance use disorder treatment program. And my support for both of these populations as a service provider, I see those patterns happening; they see substance use disorder, they shuffle those patients off.

DR. GOLDIE: Dr. Dasgupta?

DR. DASGUPTA: I think the choice of which studies to do is going to be -- is limited, or constrained at least by the practicality of very low volume products, right? So, I wonder if we can envision a submission that would have very little in the way of a formal statistical testing. Obviously, FDA uses .05 and all sorts of other parts of the statistical goings on that they can see overseas. But if we're talking about low volume drugs, would surveillance data that's well conducted with ethnographic data for a low volume drug, would that be a sufficient package to be a credible evaluation? And I don't know the answer to that question, but I'm curious how important the statistical significance in the traditional alpha equals .05 kind of way that this all hinges on.

DR. LEVENSON: No, I agree. If there is no market share you're never going to get the statistical precision. So, either there is no potential for a claim or some other pathway is necessary. This is Mark Levenson.

DR. GOLDIE: Dr. Green?

DR. GREEN: I keep coming back to the outcomes and the questions. I think a lot of stuff that we've talked about is really interesting and important in the public health broader understanding of the substance abuse and opioid abuse. So, maybe if we can parse out for a minute kind of what is of interest and informs us about public health issue versus what's required of companies under a PMR. And currently, you know, from the diagram, it's the abuse issues, addiction, overdose and death. And so if we look at that and we know we need product specificity and route specificity, then I think that kind of narrows our mosaic a little bit. But there is already, I think, some great data sources that are being used, but certainly can be improved.

But maybe we can also talk about are those the right outcomes? I think I mentioned this earlier -- addiction is probably the one that we struggle with the most, because that's not typically related to a specific product. And for a product evaluation, is that really an appropriate outcome, where the other ones, I think, fit them all a little bit better,

especially when you look at it by route.

So, certainly having the national estimates would be a nice addition, I think, to the mosaic, whether it be (unknown) or another way to do that. Because currently I think we are using a lot of the special populations, so the acute events that are reported to poison centers -- that's great because that's outcome data; the treatment centers, because that is a special, vulnerable population that's important to the issue. And then what's happening on the streets, whether it be price or the law enforcement activity, the drug diversion data, and then on the web and the chats and the forums. I like to qualify that as adding color to the mosaic. That's what I usually say about the qualitative data, because I think it is important and it tell us a lot, and it just kind of enlightens us, I guess, on the mosaic.

Probably one of the gaps, though, I still see is that patient aspect of, you know, of the patients actually getting these products, how do we track them to see what the progression is, if at all. Obviously, made complicated by the fact that typically the patient

is not just exposed to the one product, just one product; they could be prescribed more. Or, of course, they can get it from other sources. So, I would say the gap in the mosaic is that patient piece. But there's, I think, a lot of pieces that are already there that can be improved upon.

I do like the ethnographic stuff as well. One thing that hasn't come up yet is when our treatment center program, the SKIP program, one of them, our participants are asked if they would like to do follow-up surveys. And so they go into Dr. Ciccarone's RAPID program, and so essentially we have a pool of people who have intertreatment that we reach out to on a quarterly basis for special topic surveys. And so they've become a great resource. Some of the stuff has been published in terms of what did this population do when OxyContin was reformulated? Did they -- we learned that a lot of them went to the IR products, because they're easily available, easily crushable. But that was really good information. But using that population along with the field research to get at some of the special topics to supplement the other

quantitative data I think would be a nice addition to the mosaic.

DR. GOLDIE: Dr. Graubard?

DR. GRAUBARD: In listening to the two days and hearing what people are saying, I think to me there are basically three things that you should do. One is, I want to echo what was said before about case control studies. I think that would be -- I would do population-based case control studies and develop areas around the country -- find areas around the country where you have -- where you can create catchment areas where you can identify cases of overdose, whatever you want to make the case to be, in this particular case. But pick areas selectively around the country and make it clear what the catchment area is, and then draw population controls from those areas using surveys, or whatever methods are available to get population controls.

The cohort study, I agree with the previous -- Dr. Krebs, that it is going to be very difficult to do cohort studies, but I think the cohort study is really important. It should be done with a high-risk

population in the way I think she was referring to, so that you have -- and, again, it would be nice to have those cohort studies in well-defined catchment areas, where you can identify these high-risk populations. And they maybe could be scattered around the country at various locations.

My background is more population representative type analyses, but realizing that you can't do that very well here. But at least in the areas that you select, you can be representative. And you can talk about combining those results across those areas and properly weighting or proper calibration to known distributions of things from other sources, administrative databases, and so forth. Maybe you could get at some sort of population estimate.

The third thing is surveillance, and I think that we've talked about various sources of surveillance data, but population surveys is my first love. And what would be nice is to get a core of questions that you could identify that could get at the critical items that you want to build a surveillance system around, the rates, or whatever it is you're trying to

calculate. And get those questions on the major national surveys and then combine the results across the surveys. So, the National Health Interview Survey, the National Drug Use Survey, you now, there are other national surveys that could be used. Maybe even NHANES. And possibly surveys that cover noninstitutionalized populations that you could add to that to augment those samples to make it more wide population that you could actually do the estimation for. And if you have some good survey research people, they could tell you how to put the weights together properly in the most efficient way, so you can get good estimates.

That's kind of the way I would view it, but I'm not an expert in this area by any means. I work at the National Cancer Institute; I have nothing to do with this.

MS. BOSE: Just to add something to that.

DR. GOLDIE: Ms. Bose?

MS. BOSE: I'm sorry?

DR. GOLDIE: Go ahead.

MS. BOSE: Not wearing my NSDUH hat, but

wearing a survey methodologist hat, I do think there are benefits to the national surveys, because they do provide context. And I also do think that they give us numbers in ways, despite the coverage problems, despite other issues, that no other source does.

So, for example, we have a lot of expert panel meetings, and when we're mired in our particular subject area, I do think it does seem like everybody is doing it. So, whether it's treatment or any of these things. But, like, for example, when we look at pain reliever misuse numbers, they are actually not that large; they're fairly small. And so even though the NSDUH items are in some ways general, it turns out that in the nation not everybody is misusing them, whether you use users as a denominator or you use the entire population. And even if we account for measurement error, there is going to be underreporting because people don't want to talk to misusing these substances. Even if we allow for a nice, strong error on one side, just on underreporting, you still get a sense of the magnitude of the problem, what types of beginning denominators you might be looking at. And without the

national data you have absolutely no source, as far as I can tell. Because if you can look at your treatment data or users, there's nothing to say what is the magnitude that we're talking about?

And so I think that national surveys do not work well as surveillance tools, where you need to know what's happening in the now, so they don't. But I do think they just kind of, even with their coverage issues and with their measurement issues, and with their response rate issues, they do provide that kind of a basic metric. And so to build on what Barry just said is to kind of go back and say what are those key measures? And are there some key measures that are missing that are good candidates for national surveys? Because most of the stuff we've talked about potentially are not for these general, all-purpose surveys. So, what the National Health Interview Survey and the NSDUH, they're all purpose surveys meant to cover a lot of different topics. So, I think that would be one of my plugs to kind of not disregard the value of these national surveys despite the detailed questions we're asking.

And the other thing is, also, I think there has been a lot of different work done in this domain, but go back and see whether it meets your purposes. There are coverage problems where we're not including these certain populations. But what if I made an assumption of use and misuse, so substance abuse disorder rates, for example, for these populations; that would still help me establish upper and lower bounds. And so that's another way where we might use other sources along with a national source to build these overall national metrics of the population of interest that you're looking at. And then from there go into the specialized surveys.

DR. GOLDIE: Dr. Schnoll?

DR. SCHNOLL: Sid Schnoll. The case control was brought up, and I guess I have a question. How would you identify the cases? I guess part of my concern, if we're looking for overdose or death, particularly death, you would do toxicology, and you would come up with hydrocodone, oxycodone. Would you know that that was from a tampered product or another product? And so it could be a major problem. I'm

particularly thinking about and we've heard a bit about it here yesterday and today, the drugs that are most abused are the IR drugs. And it was also brought up that we got lots of polypharmacy going on in these populations. So, I'm just concerned that you would get this number, and then how would you really decide out of that group what to study and how to study it? It just -- I guess I'm confused, and if you can help, I'd like to hear it.

DR. GOLDIE: Dr. Winterstein?

DR. WINTERSTEIN: Yeah. I haven't totally designed it yet, but mortality certainly is much harder to follow up on what happened than overdoses, where somebody was rescued. Same with infections, life-threatening endocarditis or so on. We would assume that not everybody dies immediately. I mean, it would need to be a hospital network of some type, where there would be a prospective collection of those cases and then direct follow-up at admission. That would be the ideal scenario, just thinking about it on the spot. I mean, those studies certainly exist and those networks exist. It is by far more expensive to do something

like that than claims data analysis, but right now the sky is the limit. We were tagging drugs and having them explode, but mortality certainly would be much harder.

DR. SCHNOLL: I mean, would we be able to find -- we know these are rare events, and certainly right now even what we're saying in just overdoses that did not lead to mortality, a lot of it is the illicit drugs. And you may find occasionally something if you're doing toxicology. But I'd just be concerned about finding the cases and then being able to study them.

DR. GOLDIE: Dr. Graubard and then Dr. Lo Re.

DR. GRAUBARD: Yeah, so, right, deaths as already said, the deaths are hard, if they're the cases, but so you have to use other sources of information for them. You know, survivors, next-of-kin, whatever you can do. I understand there's biases and there's problems with that, but this is a hard problem and it's just not going to be perfect. We'll have people -- then you can also make inference about the cases that survive their overdoses, if that's the

identification of the case. And you can look at those -- you know, that part of your case control study. But the key is to have some sort of catchment area, where you have some sort of system, emergency rooms, hospitalizations, whatever it takes to have a pretty good complete identification of cases over some window of time, and then get population-based controls to go with it.

DR. GOLDIE: Dr. Lo Re?

DR. LO RE: Yeah, I think the beauty of the case control study is that you would fix the number of cases, so it's particularly advantageous for very rare outcomes. With regards to the outcomes that you study, you could develop and hopefully validate methods to ascertain skin or soft tissue infections, infectious endocarditis, if you wanted overdoses. And then look at associations, assuming that you've developed methods to select control, appropriate controls to look at associations between various ADF or non-ADF opioids. And so particularly if there are certain drugs or formulations that you wanted to look for the purposes of association and safety signals, that may be at least

an initial method to do that while you're waiting for these larger cohort studies to accrue patients and to get the results.

DR. GOLDIE: Dr. Scharman?

DR. SCHARMAN: I was interested in asking Dr. Brooks, is there something that we can learn from the HIV population about how to reach these special populations? I remember when HIV first came out, had a lot of stigma associated with it. I mean, your drug abusers or gays, and nobody wanted to admit any of that at that time, and yet you eventually got the place where we could do research on that population and evaluate that population. And do you have any insights on how you reached them? Because I think it kind of parallels this drug-abusing population that we could use in this situation?

DR. BROOKS: Well, I think there are probably people more expert, but what we did is we found experts who understood the kinds of people who were being infected by HIV infection as those came to light. And we didn't do studies of those people to learn to do it ourselves; we engaged those people who were expert in

working with those populations to help us reach out to them. And I think a probably a lot of people in this room have got that expertise, either from the perspective of treating addiction to medication-assisted therapy, running SSPs, running detox centers, or doing research in that area. But I would say it probably -- to design a study and to reach the right group of people, you'd want a group of experts who know about that population and how to get them, and also monitor where they are. Because particularly the injection drug using phenomenon is probably a moving target in the US right now. It's spreading into different areas. But you can follow that, and if you have enough expertise you can direct the study to where you want it to go.

DR. LEVENSON: We have a public comment session for here as well. Scott, do you want to set that up?

DR.GOLDIE: So, we're going to open up to the audience participation portion for this session. We are looking for additional ideas from the audience. If you would please come to the designated table with the

timer. Again, it's three minutes total, green, yellow, red. If you have something to contribute, please, we'd like to hear it.

MS. LEVIN: Hi. I'm Penny Levin with Teva Pharmaceuticals. Today I'm here representing the Association for Accessible Medicines, AAM, formerly the Generic Pharmaceutical Association. AAM is the nation's leading trade association for manufacturers and distributors of generic prescription drugs. AAM's core mission is to improve the lives of patients by advancing timely access to affordable generic medicines. The generic industry is an integral part of this healthcare system and believe generic ADFs can play a key role in addressing the concerns related to prescription drug abuse.

To date, the FDA has approved 10 innovative ADF opioids; however, there are no generic ADF opioids approved to the American patient with pain. This poses serious issues, including lack of access to needed affordable medicines. Additionally, drug utilization, as we've discussed the past two days, of ADF medicines is needed in larger numbers to allow both FDA and the

payers to have the data to fully assess whether ADF medicines are produced in the desired or anticipated outcomes in the postmarketing setting. While FDA requires postmarket studies to determine whether an ADF reduces the risk of abuse and misuse, no innovative ADF opioid has convinced FDA to date of such effectiveness. Similarly, payers like Blue Cross Blue Shield have stated publicly they will not reasonable the use of ADF opioids until such claims of postmarket effectiveness have granted by the FDA. Hence, this poses a serious conundrum.

The generic industry is here today to urge FDA to provide product-specific guidance to these products. Such guidance would facilitate generic manufacturers the ability to meet FDA expectations and increase access to these medicines in a more timely manner. This will also help contribute to the denominators needed in the postmarketing setting to conduct appropriate epidemiological studies.

It is important that while the Agency has historically looked at the risk of abuse and misuse in the drug abuser, we cannot lose sight of the true

patient who suffers from pain. We may want to step back and ask ourselves, if we are not able to understand whether a product is deemed effective or not from an ADF perspective after collecting and reviewing data from numerous postmarketing studies, are we asking the right questions? Are we collecting the right data to make such a determination? How are we viewing success and how are we measuring it? These are very difficult issues, but important questions to ask, and appreciate the FDA and advisors' thoughtful and comprehensive approach they have been taking to understand this complex area.

In closing, we urge FDA to reconsider their hypothesis of solely identifying success as a reduction in abuse and misuse by the drug user and instead consider the following questions: Have all of the relevant stakeholders been identified and are they engaged? Are we asking the right questions to capture effectiveness of an ADF? Are we collecting the right data to evaluate the effectiveness of the ADF, and how are we measuring success? We welcome to the opportunity to discuss this important matter with the

FDA and will provide comprehensive written comments to the docket. Thank you.

MS. NIEBLER: Good afternoon. I am Wendy Niebler with Egalet. I appreciate having the opportunity the past two days to listen to the discussion and to comment. Yesterday and today there was a brief discussion of the study challenges giving the low prescribing rate of most abuse-deterrent formulations of opioids. I would like to reinforce this point. For example, in 2016, over 97% of prescriptions for morphine were for nonabuse-deterrent formulations despite there being an abuse-deterrent formulation available on the market. We can have the best study designs and analysis plans, but real world studies cannot be conducted successfully if the low prescribing of ADF opioids continues. Healthcare providers need to be encouraged with multiple methods, including policy, to prescribe the abuse-deterrent formulations if they decide to prescribe an opioid. In addition, payers need to understand the importance of coverage of these products on their plans and the significant role they play in obtaining the real world

data we all desire. Thank you.

DR. POLANIN: My name is Dr. Megan Polanin. I'm with the National Center for Health Research. Our center analyzes scientific and medical data and provides objective health information to patients, providers and policymakers. And I do not have any conflicts of interest. We greatly appreciate the FDA's efforts in holding this meeting to discuss data and methodological strategies to evaluate the impact of ADFs. The presentations and panel discussions have been stimulating and informative. With next steps in mind, one proposed strategy we want to reinforce is utilizing correct nomenclature to describe opioids with ADFs to ensure that they are accurately prescribed to and used by patients. For example, if a drug is difficult or impossible to crush, it can be labeled as crush-resistant instead of abuse-deterrent. If an opioid is determined to be more difficult to crush, a study could compare various warnings on labels for the drug to see which, if any, are more effective. Labeling a drug as crush-resistant instead of abuse-deterrent may result in less abuse. We believe

providing scientifically accurate information for doctors and patients is a critical factor in preventing opioid misuse and abuse. Thank you for the opportunity to share our perspective.

DR. COPLAN: Paul Coplan, Purdue Pharma. Firstly, with regards to the controls for case control study, so the controls are intended to reflect the prevalence of use of the exposure of interest in the population that gave rise to the cases. So, Dr. Graubard talked about using a population-based control, but the population would not be using opioids to the same -- so, if we look at overdose as a -- you know, overdose cases. And then we're looking for controls that reflect the exposure to an abuse-deterrent opioid. So, if we use population-based controls that wouldn't be using opioids, so there would be less exposed to opioids, so it wouldn't be reflective of the prevalence of ADF use in the population that gave rise to the cases. So, would it be, then, a population control in opioid users, I think which is what Tara Gomes did in the slide that Dr. Meyer showed.

And the second thing had to do with there was

some discussion about numerator-only datasets, and I think the poison centers -- sorry, the treatment centers were considered numerator-only datasets. And then we heard Dr. Brooks and Dr. Budnitz talked about high risk samples, so subsamples of high-risk populations that you could look at to see where, when the abuse-deterrent formulation came into -- what was intended to be abuse-deterrent -- when it came into those populations, was it abused or was it not? And then Dr. Throckmorton referred to that having a high power, better power with a small sample size to be able to pick up a signal. And in fact the numerator-only samples could be considered subset or subpopulations of high-risk groups. So, for example, treatment centers are in fact like a sentinel population of the type of population that Dr. Brooks is talking about. It has the advantage of systematic evaluation by the same questionnaire over time, so you can look at trends over time. So, I just wanted to share that thought. Thank you.

DR. DEVEAUGH-GEISS: Hi. Angela DeVeaugh-Geiss, also from Purdue Pharma. I just -- I thought it

was worthwhile to reemphasize something that was brought up during the last panel discussion, which is that we've got research designed to address the broader public health question of opioid abuse and related outcomes. And then we've got the PMRs, and within the PMRs we even have two kind of distinct pathways. We've got the ER/LA opioid class PMRs, which have been discussed throughout the day with some examples of the prospective cohort study provided during, I think it was Dr. Kornegay's talk this afternoon. And on a separate line of work, to some extent, we've got, then, the individual product level postmarketing requirements designed to look at the effect of the abuse-deterrent formulations. And as we're talking about study designs, there has been a lot of interesting options brought up, but I think it's important to remember that each group is really distinct and would have a different study design that would be best to answer the questions of each kind of program of research. For example, with the abuse-deterrent formulations, if the goal is to look at whether there is a real world effect on insufflation and injection, we need to be sure that

whatever data we're using is able to get to that level of specificity of the outcome, as opposed to a study like the prospective cohort study for the class PMRs, where we're actually looking for instant abuse and misuse among individuals initiating therapy with ER/LA opioids, again, which is a very distinct behavior. Within that you may have injection and insufflation, but it's not the end all kind of metric that we're looking for.

DR. GOLDIE: Are there any other audience participants for an oral presentation? Okay, with that, then I'll close the audience participation component and remind everyone in the room that additional comments and information can be submitted until September 11, 2017 to the docket. The docket is on the screen in front of you. And I will turn it over to Dr. Staffa.

DR. STAFFA: Any -- I'm going to ask the group -- any final comments or thoughts, knowing that these don't have to be final comments; they're just final comments for today. As you go home and noodle about this and think it over and thoughts occur to you,

please, send them to the docket. Again, we're very, very interested in hearing all and any ideas as we work through this, and I'm sure our industry colleagues are very interested as well. Any final comments for today? Oh, Dr. Racoosin?

DR. RACOOSIN: Hi. I'm Judy Racoosin. I'm the deputy director for safety in the Division of Anesthesia, Analgesia and Addiction Products. We're the division that is responsible for reviewing and helping to guide the development of these products that have been the topic of the meeting for the last two days. And I just wanted to thank everyone for all of your participation and comments. My colleagues in the Division of Epidemiology and Biostatistics have been leading the methodologic in discussions that have happened for the last two days, and I will be looking forward to collaborating with the groups as we move forward to figure out what these study designs are going to look like. But I just wanted to take a moment from the review division perspective to thank you all for participating.

DR. STAFFA: Yeah, and I think on behalf of

all of us at CDER, I know many of you took time out of your busy schedules as well as your summer vacations to join us and to provide your considerable expertise. I think we got a lot of questions at the beginning when we were inviting you to this meeting of why are you inviting me to this meeting? I'm hoping it's clearer now why we invited this very eclectic group, and I have to say we have truly benefited from the conversation you stimulated, even when I got up in the stratosphere, it's been fascinating, and you've given us a lot to digest. So, thank you very much for your participation and we hope to hear more from you from the docket. Thank you, and safe travels.

(Whereupon, at 4:10 p.m., the workshop was concluded.)

CERTIFICATE OF NOTARY PUBLIC

I, MICHAEL FARKAS, the officer before whom the foregoing proceeding was taken, do hereby certify that the proceedings were recorded by me and thereafter reduced to typewriting under my direction; that said proceedings are a true and accurate record to the best of my knowledge, skills, and ability; that I am neither counsel for, related to, nor employed by any of the parties to the action in which this was taken; and, further, that I am not a relative or employee of any counsel or attorney employed by the parties hereto, nor financially or otherwise interested in the outcome of this action.

MICHAEL FARKAS

Notary Public in and for the

State of Maryland

CERTIFICATE OF TRANSCRIBER

I, SANDRA TELLER, do hereby certify that this transcript was prepared from audio to the best of my ability.

I am neither counsel for, related to, nor employed by any of the parties to this action, nor financially or otherwise interested in the outcome of this action.

7/23/2017 Sandra Teller

DATE SANDRA TELLER