UNITED STATES FOOD AND DRUG ADMINISTRATION
CENTER FOR BIOLOGICS EVALUATION AND RESEARCH

POST-LICENSURE RAPID IMMUNIZATION SAFETY MONITORING (PRISM) PUBLIC WORKSHOP

Bethesda, Maryland

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(8:44 a.m.)

Session I: Welcome and Introductory Remarks

DR. OBIDI: Good morning, everyone. We're going to start. I wanted to thank you all for coming. Welcome to the PRISM public workshop. Before we begin, I wanted to go over some logistics for the meeting. The first thing is, as you saw when you walked in, there's a big sign that says "No food. No drinks," and that's a very strict rule. No water, nothing. We have a table outside for you. You can put your drinks out there. There's markers if you want to label it. There's also a café downstairs, so if you want to get coffee or snacks in between, you're more than welcome to go downstairs. There's a bathroom -- when you came in, and you saw the registration table, there's a bathroom right next door. I wanted to let you all know that we have a very packed agenda. As you can see, we're starting a little late. For the speakers and the panel members, it is very important that you stick to your allocated time. We have a timekeeper right here. She is going to let you know how much time you have left, so that's very, very important. For the audience members, please hold your questions until the end of each session, and –there is a mic at each one of your seats, there's a button for the mic. Press that when you want to ask a question, and when you're done, just remember to click it off so that there's no feedback. To open our meeting, I'd like to introduce Dr. Steve Anderson. He's the Director of the Office of Biostatistics and Epidemiology and the Center for Biologics Evaluation and Research. Welcome, Dr. Steven Anderson.

DR. ANDERSON: All right. Well, thank you. I think the first thing is to welcome everybody, and thank you for participating in our first PRISM workshop which stands for Post-licensure Rapid Immunization Safety Monitoring System and I'm not going to be repeating that much throughout the session because it's, sort of, a mouthful. We'll just be calling it PRISM throughout the session.

I thought I'd start with a little bit of history about PRISM. For some of you, this may be familiar; for some of you, not. So PRISM was started in 2009 in, sort of, an inner government, inner institutional program that arose from the need for safety surveillance and improved safety surveillance during the H1N1 pandemic. A year later, in 2010, the system was rolled into the mini-Sentinel system which is FDA's pilot system for what would become the Sentinel program. In 2015-2016, Sentinel was stood up along with PRISM and our blood scan programs that are part of CBER, Center for Biologics Programs. Just to mention, the Center for Biologics has regulatory authority and responsibility for vaccines, blood and blood products, and cellular tissue, and gene therapy. Keep that in mind we are not the center for drugs, we are the biologics people.

What I want to say about PRISM is, in this, sort of, six or seven years, we've really come a long way. Prior to PRISM, I felt like we were, sort of, in the dark ages. We had the

vaccine adverse event reporting system to tell us about potential vaccine signals, but we didn't have denominator data and a way to basically assess rates of adverse events. We did have access in some limited ways to the vaccine safety data link through collaborations with our colleagues at CDC, but it really wasn't our system that we could use on a regular basis. When Sentinel came along, when PRISM came along, for us it was really a game changer in the way that we did business. We now had -- FDA had its own system by which it could evaluate regulatory questions and use the system to evaluate those regulatory questions on a more regular basis. It was, sort of, a go-to system that we ask, sort of, informal questions to again related to anything that came up in the regulatory setting.

I wanted to just also mention that the system has value to a lot of us. It's a system that, in many cases -- prior to the system, we wouldn't have done a study necessarily, and now we have this system where we can do studies that have public health impact. The other thing is, I think value to sponsors and manufacturers. Instead of asking sponsors and manufacturers to do a study, we're taking on several of those types of studies in the Sentinel/PRISM system. That's the value, sort of, added with the system.

As an overview for the workshop, I just wanted to give you a sense of where we are with Sentinel and what's it's comprised of. We've built a data infrastructure system with Sentinel. You're going to see varying different numbers, but it's approximately 190 to 200 million persons that the system covers. That's the data infrastructure. The second part of that is the method. We have, sort of, a methods toolbox of a variety of tools that have been developed, as well over time. One of those is the active risk identification and analysis set of tools, or the so- called ARIA tools. You'll hear a little bit more about those later. We have Tree Scan, we have scan statistics, and a variety of other tools that we've developed over time that can be more readily used to access data, and to conduct small types of studies.

The other thing is, these tools can be used for larger studies. For instance, we do mostly in the Center, we're doing large protocol base assessments when we're studying vaccines. Those are studies that are large epidemiological studies; pretty comprehensive in nature. In addition, we're able to do some rapid quick queries using the ARIA tools. If we say, somebody from a foreign source identifies a safety signal in a vaccine, we can query the system and say, okay, are we seeing the same thing in that vaccine, and that adverse event in the Sentinel system. We can use it to actually do, sort of, a feasibility to figure out, is there a signal there? Are there cases there? Is that something we should follow up with further studies? The Sentinel system, the quick query system, allows us to do that.

As far as regulatory accomplishments over this past several years, the regulatory accomplishments have led to a labelling change using the system, a safety communication and then communications of study findings in other ways. Again, we're using the system also to do these, sort of, quick analysis to address questions, so that's an accomplishment in and of itself, as well.

You're going to hear a lot today about the work that goes on behind the scenes that you wouldn't necessarily be aware of unless there was this type of workshop. Where we're going in-depth into the types of methods and the activities. This is a coordinated effort. I will say on our side, it's -- in CBER, it's a function of our work between the Office of Vaccines and my office, the Office of Biostatistics and Epidemiology closely working with Harvard Pilgrim and -- or the so-called Sentinel Operations Center and their staff. They have a staff -- that number is quite large, 60 or so people. This is a very large effort, and I have a fairly large staff that's devoted to this, as well. Just get that feel throughout the day, that this is a really a large effort, but an important effort.

What's our main objective with the workshop? Our main objective is to start doing outreach on the program. We felt that transparency's important so it's, sort of, like the real estate mantra: transparency, transparency, transparency. We're trying to be proactive in that respect in conducting the outreach, and this type of workshop really feeds into that type of activity. We sincerely want to hear people's opinions, the panelists' opinions about the programs. Do we have the right priorities? Do we have the right priorities going forward? Are we doing things the way they should be done? Do you have further ideas about where we should go in the future? Please feel free during the course of the day to bring up points and provide us with that feedback.

The goals of the workshop are really to showcase the capabilities of the Sentinel program. Another goal of the program is really -- of this workshop is to communicate with stakeholders about the PRISM program and gain feedback from you, that's going to largely occur in Session V. Our goal in that session where we have a lot of stakeholders on the panel, again we want an open dialogue to hear their thoughts about the program.

Then the third point is really to discuss the PRISM program priorities and future direction. What does that mean? Well, we have two sessions where we want to talk about things that are, sort of, moving towards future directions and things that are in development phases. The first one we want to talk about is Tree Scan. We haven't been using the system a lot for signal detection. We want to move in that direction. We're going to be talking about that Session IV. Again, how can we use this tool called Tree Scan to actually start doing more signal detection?

The other part that's, sort of, new to us is conducting effectiveness work. We've been conducting effectiveness work. Dr. Hector Izurieta's been doing a successful job doing work in CMS, looking at influenza vaccine effectiveness. We can do that work in Sentinel, as well. During that session, I just want to reiterate that this is really developmental-type work. We're trying to figure out where does this fit in the regulatory process. We hope to have during that session -- which is I think it's Session VI -- a robust discussion about how we're going to be using effectiveness work in our regulatory work.

Then finally the closeout is -- or the next to the last session will be Dr. Rich Platt who will be talking about access to the system. How can other stakeholders have access to the system? Again, it's another -- it's another important part of this. I think the grand vision

for Sentinel is that it is part of a large national data infrastructure and network of data, and that it's a resource that others should be able to use. During the session, we're going to be talking about that. Again, the overall themes that I want to just emphasize throughout the day are the priorities for the program which is really pandemic response, going back to the roots of, you know, where the program started, talking about vaccine and adverse event signal refinement which is another important part of the work we're doing. Vaccine safety and maternal immunization safety, it's a huge part of our portfolio. Then vaccine adverse event signal identification, getting into the -- moving into the Tree Scan part. Again, these are, sort of, the themes, and again we want, sort of, robust discussion, comment, and feedback on these throughout the discussions.

We're proud of the program. I just wanted to, sort of, end with the funding and where that comes from for the program. The funding for PRISM comes largely from CBER's operating budget, and the user fees for Prescription Drug User Fee Act. Our big benefactor is Dr. Peter Marks. We're thankful for the funding that we have to do this work because it is as significant amount of funding that's needed to keep this program afloat. I also wanted to give thanks to my colleagues in Office of Biostatistics and Epidemiology, Office of Vaccines, Research and Review. Then Harvard Pilgrim, as well, for their help in getting this program off the ground, but also in helping organize this workshop. Then I wanted to thank Azadeh and her -- Azadeh Shoaibi who is the CBER Sentinel lead -- and her group. Joyce Obidi, and then also Kinnera Chada who've done really the work (inaudible) in, sort of, bringing this together. That's the end of my comments, and with that I'm going to go ahead and introduce Dr. Peter Marks for his comments. Dr. Peter Marks is an M.D., Ph.D. He is the FDA's Center for Biologics Evaluation and Research Director, and he's going to make a few comments. Thank you so much.

DR. MARKS: I'm going to try to get us back on time. I was stuck in getting through the security line for a while there, but made it through as we were all were -- no, no, that's right. I'm only going to cover some issues as it's just since Steve really covered most things. The true benefactor here is the -- is the user fees that need to do this work, but I just want to thank you all for participating in this workshop. It's interesting to reflect right now that I'm going to take the larger view here, that the reason why this work is so important is because right now confidence in vaccines is important. Maintaining confidence in vaccines is important as it ever has been. For whatever reason, despite the fact that it is -- it's unambiguous that vaccines are perhaps -- well, depending on -- you can argue, is it sanitation? Or is it vaccines? But one of the two are probably among the most important public health measures that have been instituted in the 20th century, and continuing into the 21st century. Yet we still have tremendous concern regarding the safety of vaccines, or questioning whether vaccines cause all sorts of other things. Having a system that really makes us confident, that we understand the safety profile of vaccines is absolutely critical. You know, really ultimately this program, the PRISM program has really exponentially

expanded our capacity at the Center for Biologics to monitor the safety of vaccines and utilize these capabilities for broader regulatory purposes. Also to help reassure the American public that vaccines are safe and effective -- safe in their efficacy. We hope that today's gathering will provide an opportunity for all of us at CBER, and others who are joining us, to have an open dialogue and this will, I think, be a very nice time to speak with all of the various stakeholders about the PRISM program. Its limitations, how it could be expanded and how it could be refined. We look forward to the discussion today. I will try to get us back on time by concluding and I wish everyone a very successful day. Thanks. (Applause)

Session II: Laying the Groundwork: A Sentinel/PRISM Overview

DR. OBIDI: Now we're going to move onto Session II, which is laying the groundwork for Sentinel and the PRISM overview. I'd like to introduce Dr. Azadeh Shoaibi. She is the Sentinel lead for CBER, and she's going to give an overview of Sentinel and the PRISM program. Please welcome Dr. Shoaibi.

Sentinel/PRISM Program Overview:

DR. SHOAIBI: Thank you, Joyce, and thank you folks for coming. As Joyce said, I will be providing some short remarks about the Sentinel initiative and the PRISM program. I'll just start by talking about the Sentinel initiative to orient everyone to where we are, and then the component -- the vaccine component of the program which is PRISM and some of the characteristics, and current priorities of the program.

As some of you, or most of you are aware, FDA Amendments Act of 2007 required that FDA establish an active post-market risk identification and analysis system in order to link and analyze safety data from different sources. These sources were required to include both public and private sector health-related electronic data. The objective of the Sentinel initiative was to enhance FDA's capabilities to identify and be able to investigate safety issues more in the near real-time manner. Also to investigate issues that could not be easily investigated using the passive surveillance system that was in place at the time. The Sentinel initiative was also tasked with providing data for subgroup populations, for longer-term individual, longitudinal availability of data. Also to investigate adverse events that would commonly occur in the general population, but because they were common occurrences, they would not necessarily be reported to FDA through the passive reporting system.

As Steve mentioned, FDA's vision for the Sentinel initiative has been to build a national data infrastructure for evaluating medical products safety, and make that available to FDA, as well as to other stakeholders.

PRISM again stands for Post-licensure rapid immunization safety monitoring. I'd like to just mention briefly the origin of PRISM. Again, as Steve mentioned, in 2009,

Department of Health and Human Services created a national system for monitoring the H1N1 pandemic influenza vaccine. The objectives of that program were to have data available for a large population, to be able to capture rare adverse events, and also to capture the administration of the vaccine -- H1N1 vaccine -- in many different settings. The data sources included National Health Plans and state immunization registries, and the program was led by the National Vaccine Program office at the HHS, along with FDA, CDC, Harvard, and America's health insurance plans.

The program was built in 2009-2010, and there were some capabilities of access to data for a large population. The decision was made not to disassemble what had been built and had certain capabilities, but to roll it over to the mini-Sentinel program. Which at the time was the pilot phase of the Sentinel initiative, to sustain and maintain program in 2010. PRISM became the vaccine component of the mini-Sentinel and later on, Sentinel and since then, CBER has been working very hard to build this system into a vaccine safety surveillance system and to be able to perform safety studies for a variety of vaccines, in addition to the flu vaccine.

It should be noted that PRISM was built on the successful experience of the vaccine safety data link as a safety surveillance system. VSD was established in 1990, and has been a successful program led by the CDC, VSD utilizes electronic health records. PRISM utilizes administrative and claims data for the most part. We have a very small proportion of our data coming from electronic health records, but for the most part, our bread and butter is claims and administrative data. PRISM covers a larger population, significantly larger population. But from the beginning, the agreement between PRISM and VSD was that PRISM would use national health plan data, and not data from the organizations that were participating with VSD. We have kept that promise.

Just to orient you to the relationship between PRISM and another program at FDA, led by a FDA and CDC called VAERS, which is Vaccine Adverse Event Reporting System -- is that with the capabilities about PRISM that you will hear throughout the day, it is an active safety surveillance system. VAERS system is -- with its capability, is basically a passive surveillance system, but each one of these programs contributes certain stream of evidence to the pharmaco vigilance toolkit that FDA and CBER have available. Each one has its own contribution and PRISM is not going to replace VAERS.

I'd like to shift gear here and just very briefly talk about some of the basic, but fundamental, and very important characteristics of the PRISM program and the capabilities that it has provided for us. We have access to denominator data as Steve mentioned before, and we have access to the denominator data for vaccine exposure. That capability alone allows us to estimate a measure of association between a vaccine and adverse events which is a huge capability which was not readily available to CBER prior to having the PRISM program. PRISM has other capabilities and characteristics. It covers a very large population of the country. We have longitudinal data available for, again, a large population. I think on average, each individual contributes two to three years-worth of data to the PRISM

database. Also, although there is a lag in the data that we have access to at any given time, our data is still relatively recent. These characteristics, along with the capability to estimate a measure of association provide capabilities for this system to become an active surveillance system. These characteristics altogether fulfil the requirements that FDAAA set up for FDA to build that active surveillance system, and to link and analyze the safety data, and to utilize the information from the system for regulatory decision-making.
Sentinel initiative which is the larger umbrella program for the PRISM, currently has a team of data partners contributing data. Based on the agreement between VSD and PRISM, we use a subset of those data partners for our PRISM and vaccine studies. There are four large health insurers that contribute data to PRISM. They include AETNA, Health Core, Optum, and Humana. Their data that we have access to starts in 2006 to the present time. There are also two smaller organizations that contribute data to PRISM. They include Harvard Pilgrim Health Care Institute, where our operation center is located, as well as Vanderbilt University Medical Center. Their data starts in 2000 to the present time. Overall, these organizations together have access to data for approximately 190 million individuals. Of these total number, approximately 30million individuals are currently enrolled in the program and contribute data at the current time.
I think Steve mentioned the priorities for PRISM. PRISM has concentrated in a few areas from the beginning of its activities. One of the areas is signal refinement and evaluation for a specific vaccine and adverse events. We have completed a number of projects in that area. We have recently embarked on signal identification activities for a specific vaccine and a large array of adverse events. Pandemic response is certainly a major focus. Then vaccine safety in pregnancy is also one of our major concentrations.
There are three types of activities that we usually conduct in PRISM. We have to build the infrastructure. An example of that are the rapid query tools that have been built to be able to query the data very -- relatively quickly. Development of methods and the signal identification method called Tree Scan is an example of that. We have completed a project for Gardasil vaccine, or human papilloma virus for quadrivalent vaccine. Then we have the infrastructure and methods, we are able to look at specific vaccines and specific adverse events and their associations. An example of that is rotavirus vaccine and intussusception.
In summary, PRISM program as the vaccine component of the Sentinel initiative provides active surveillance capabilities for FDA to be able to evaluate and answer many safety questions in a faster manner in the post-market study. Using our rapid query tools, which formerly were known as module programs, along with the customize protocol- based assessments, we have done a variety of safety activities. Overall, this shifts some of the burden from the sponsors.
I'd like to acknowledge a large group of people who have made this work possible including our operation center, my colleagues at CBER, data partners, and our Sentinel investigators and collaborators across many institutions. Thank you. (Applause)

PRISM Infrastructure and Capabilities:

DR. OBIDI: Thank you, Azadeh. I'd like to introduce our second presenter for this session. Dr. Jeffrey Brown is the Chief Operating Officer for Sentinel at Harvard Pilgrim Health Care Institute. He's going to talk to us about the PRISM infrastructure and its capabilities.

DR. BROWN: Thanks so much. Boy, H1N1. I remember the phone call for H1N1. That was a fun time. It's actually really nice just -- first, thanks for having me. That was a great presentation, Azadeh, but CBER -- Azadeh and Steve for leading this, having this meeting, I think is really important. It was fun to think back from H1N1 and the fun activity, the craziness that went on when you, kind of, start and realize we have to build something, we got to build it now, and we really don't have the infrastructure to go -- to think about what we have now as an infrastructure. It's really pretty special, how we've gone from there not that many years ago to now. Essentially, it's been one administration is really how it's played out.

I'm going to do -- I'm still thinking about overview, to really trying to set the stage for what the presentations to come. The presentations to come, we'll be diving a little deeper into the actual work that people are doing. I'm trying to present, kind of, the framework of PRISM and how it sits inside Sentinel. Really the infrastructure is shared, it's how we think about it. It's made -- it's allowed FDA to really leverage a lot of work when you take a couple steps back. The way we had to think about building infrastructure and the tools, is it really different to find a vaccine exposure and an outcome within x number of days, or a drug exposure and an outcome with the next day. Why don't we build tools that can do both, so we're able to, kind of, leverage infrastructure as we're going along. I'll be talking about PRISM. I'll try to make some differentiations between PRISM and Sentinel where they -- where appropriate. My conflict -- I don't think I have any conflicts for the presentation, although I'm funded by public and private. I have a nice consortium of public and private funders.

Azadeh mentioned how this really started -- of this -- the FDA's Amendments Act mandate to create an active surveillance system -- actually had numbers in there -- 25 million by 2010, and 100 million individuals by 2012. We've met that and gone well beyond.

The -- and Azadeh went through this. The things that I'll note is, that we operate under FDA's public health authority. What does that mean? It's actually incredibly important that we were able to bring this about. That means that these -- we act as an agent of the FDA. We do not get IRB approvals for these projects because we're not doing research, we're acting as a public health agency. It really streamlines a lot of the work we can do because you can imagine if you were going through, kind of, the full regulatory system of IRB every time we wanted to ask a question, the whole benefit of doing it quickly, kind of, ceases to exist. It's just harder to do it that way. It's really important that we push that

through very early, and Sentinel, kind of, made that -- were able to get that to happen. The -- this is really -- I wanted to give a visual of how we organize ourselves in Sentinel. Harvard Pilgrim, we're the lead institution so I sit inside Harvard Pilgrim Health Care. The contract comes through us, so this is the Sentinel contract -- the PRISM contracts, I won't go through all the different mechanisms of how it plays out -- but it comes through us. We have a set of subcontractors essentially. These are -- we think of them as our incredibly important partners. We have about 30 subcontracts that make this work. We've split them into data and scientific partners -- and scientific partners -- just the differentiator being the data. The folks who are bringing data have different needs and requirements, than the folks bringing science expertise. The way I'll think about it, we have this middle layer of data -- this is Sentinel. I'll just go to the next slide to circle the four big data partners these are actually the four big Azadeh mentioned -- Harvard Pilgrim and Vanderbilt. They're also part of the PRISM partners. The -- we have data partners bringing data and their scientific expertise. We have scientific partners who bring expertise in -- it might be clinical expertise, epidemiology, data science. It really can be anything, but they -- it's important to know that it's a full ecosystem of folks who are at the ready to help with this work. It's not a small group, even though it's actually a pretty big group now in Boston that does this. We really have the ability to go all across the country to find the best people to be able to do the work. It's -- one, it's been important for Sentinel and for PRISM; and two, I think the other piece I just want to bring out here is the partnership with the data partners. It's really been special that we can -- I'll probably mention us a little later -- but the idea is, if we see something in the data that raises a question, or looks a little unusual, or it looks a little funny in 2012. We can pick up the phone and call them, and they either have the answer because they knew about it, or they can go back into their systems and get the answer. It's a really special relationship that makes the value of this network is so much -- so much better because of this relationship with those partners.

Sentinel is set up as a distributed network. What does that really mean? We don't have any data at the operations center in Boston -- we don't have a big database. Our data partners keep the data behind their firewalls. They have full control over their data. We're not asking them to send their entire data sets to us. We don't really want them, so they keep them. It's fully under their control. What does that allow? One of the important things it allows is, we only get the information we need for the analysis we're doing. It's -- that's this constructive minimum necessary, and I think Sentinel's -- and Sentinel/PRISM have pushed this construct of minimum necessary really farther than anyone else that I've seen. If all you need to know is the rate of vaccination by age and sex, you don't need someone's entire medical history to start flying around the Internet, when really (inaudible). You only need a little bit of information. That's all you need, so that's all you get. We've really pushed that envelope with our tools. It's also patient privacy. It really does protect patient privacy, when you leave the data where they sit, and

you only get the information you need. Also our institutional proprietary interests, which are the interests of our data partners. These national insurers -- proprietary interests -- where they would rather -- maybe their competitor not know something about their population, where it sits, or how it's changed over time. We want to protect their interests, as well. This allow -- this distributed approach allows all of that.

Problem is, it makes doing the work a little bit harder. If I don't have a database that I can -- a big database to work with, how do you figure out how to do the work? As I mentioned, it's a distributed architecture. The way we implement a distributed architecture -- there's other ways of doing it. We ask the partners to standardize the data, so all of our partners have data that look the same. I'll mention a little bit more about this later. Again, the partners maintain that physical control of it. They control all the uses. They control all the transfers of the data, so nothing leaves their building unless they say so. I'm mentioning these because there are distributed architectures where the data remained distributed, but you're allowing someone to, kind of, poke in, run a query, and grab data, and pull it back out. That's not how this is working. It's very -- it's asynchronous in how we do this query. That's by design because it keeps our data -- well, no one -- we wouldn't do it any other way. Our partners wouldn't agree to do it any other way, but we think it's actually a better way of doing it. We distribute these programs. We distribute analytic programs to our partners. We use secure software called PopMedNet that runs inside their firewalls on that data, and they only send back what's needed. I -- this last point, I'll note, this was a requirement the program executes without modification. We're actually running the same piece of code everywhere. We're enforcing that we're doing the same analysis everywhere which is -- it's an important piece of how we do this.

This is our visual of it. We really do log into a website. Once we figure out the query -- and I'll talk about the queries in a sec. We log in. We distribute it to our partners. They pull it in to their system -- that's in the middle -- so it goes through -- they pull it into their system. They execute it. They get to review the results. In fact, when they're reviewing the results, it's another added value because sometimes they'll look at it and wonder, you know, why are there so few people in this query? Or why is it look a little weird in 2016? It actually gives some value because they're reviewing the results. Then they release them back to us, back to the coordinating center through the secure portal, and then we aggregate results and then present them back to FDA.

As I mentioned, the way it works, there's a couple pieces that make this type of network work and the foundation's the common data model. We've asked our partners, we've developed over -- about 12 to 15, or 16 months in the beginning of Sentinel -- we developed a common data model with all of our data partners together. As Azadeh mentioned, this is mostly claims and administrative data. If you're familiar with a claims database, it should look a lot like a claims database. It has the characteristics of one of those. We've organized it -- and enrollment -- I'll only pause here for a second because the

construct of a denominators come up several times -- that's the enrollment. Health plans have this nice benefit of having a start date and an end date for enrollment. Between those times, we should see all medically attended care. That's why we think we have a denominator. Said another way, if you don't see care between that start date and end date of enrollment, it probably didn't happen. We're not -- we don't think we're missing important medically attended events. Demographics don't run particularly deep. Outpatient dispensing are really nice -- so that's outpatient pharmacy dispensing. Then on the -- the last few, think medical encounters -- every medical encounter, there's an encounter and during that encounter, you might have diagnoses and procedures that are associated with that encounter. We just organize them this way to make it easier for the analytics, but you just think it's a medical encounter information -- which really what you're thinking.

We do -- excuse me -- some of our partners do routinely link to state death registries, so we'll get death and cause of death. We have all the limitations of linking to a state registry, so the data are a little bit old -- but you -- but some of our partners will have it. I included the state vaccine table here, partly as a reminder of all the work the people did to create that table and do some linkages to it. It's not routinely updated. We do not go link to state immunization registries on a routine basis. We have done it and you could do it. It's a big deal to do which is why it's not done routinely. Some of our partners actually have some clinical data, and for the PRISM partners -- think -- there are some lab results that are available for some of the PRISM partners. That's portions of the -- portions of our PRISM partners -- patients have lab data.

I won't go through this. The idea is, if we're going to ask our partners to create this common data model, well, then we have to make sure that the data are the same at all the places. They're organized the same way, so we have a very, kind of, robust data quality assessment process. Every time the data are updated, we check to make sure that the data have been updated in the way we expect. If we see something interesting or unusual, we'll call the partners and we interact with them until we approve the next refresh. We do 50 to 60 refreshes a year on the data from - - across all the data partners.

As Azadeh mentioned, so you have the framework of this common data model, and now we have something we call as the routine analytic framework. Azadeh mentioned modular programs. If you have this data -- this standardized data - - it gives you the ability to create tools to use it, so we can ask questions quickly. That's the trick. You have to - - there's no reason to do the data model if you can't get at it quickly. We've built a set of routine tools where we have something we call modular programs that really takes days or weeks to get an answer and the variation -- and it can -- the variation really is, how long does it take to make a decision of what you want to ask? But once you figure out the question, it really can take days or weeks to get an answer. That's -- you can't short-circuit the epi or the question. That you have to take as long as you take, but then the idea is, once you figure that out, it should be quick to get some information.

We have another way we do this work now, which is modular programs plus a little bit of ad hoc coding. If the modular program get you most of the way there, but you just need one new thing, we can, kind of, add some coding to it. That takes a little bit longer because we're writing new code. Then we do protocol-based assessments. You might think of them as an epi study. Develop the protocol, post the protocol, comments on the protocol and you just -- it looks like a study. The benefit of doing that study within this environment is the study is still based on a standard data that's already been checked, already been quality controlled and you can use the tools as appropriate. You're not starting really from scratch when we're doing even these protocol-based assessments.
Now we do have a toolbox. We think about it -- there's a lot of different things that we can do within Sentinel and PRISM. Against -- these tools work against the data, so you can use it for whatever purpose you want. Exposures during pregnancy can be medication exposure, or it could be vaccine exposure. Doesn't matter to us, it's a code so we built the tools to be able to do both. That's actually a new -- a new capability. Now, I circled this one because it's really the workhorse. Because a lot of what we do is define cohorts using precise inclusion/exclusion criteria and other -- and other kinds of criteria, and then do something with those cohorts. Either just explain them, compare them to each other, propensity score match. You can do lots of things, but that -- finding the cohort is repeatable. We've spent a lot of time making that piece of -- that tool work very well.
I'll quickly go through this. The idea here is just a visual. The way we think about doing the work is you identify these cohorts. We built a tool to do this, so we're not doing this from scratch every time, and then what do you want to do with it? This is just an example of the propensity score match tool. These -- all these things -- the reason we started to call these modular programs is because they really do fit together. You tie them -- one leads into the other is how we do it. The reason I'm bringing them up is because it enables us to get at the data quickly, to get answers quickly. We built all these so we can go more quickly. Anytime we develop a new program, we go through a whole -- a development of standard -- new program development SOP. This just means that if you're going to work in an environment like this, it's a little bit different when we send a PRISM request out to our partners, and it might go to four or it might go to six partners. If it -- if we made a little mistake in it, we've now wasted the time of six partners. We spend a lot of time making sure the programs work upfront because when we send it out, it's just a bigger issue because we have more people involved. If you're sitting in your office and you have a database, and you write out -- you make an error, or you change your age categories, it only hurts you. You ran the program and then you just run it again. When we do it, it goes out to all of our partners, and they have to run it. Then we have to say, oh, don't worry -- and run it again. We spend a lot of time making sure what we send is actually what we want. It's a little bit different. I'm mentioning it because it's different -- because it's a distributed network.
New analytic capabilities. There's really two ways we think about adding capabilities, or

analytic capabilities in Sentinel. There's the continuous improvement cycle. We have tools; they work; they do a set of activities. But through use, we can make them better and sometimes this is just make them run a little bit faster. Can you change the way the output looks? We're always changing the tools in small -- using small modifications. I wouldn't say -- it's not a completely new feature of -- or new capability, but you're making it a little bit better. It's often based on feedback from FDA. I'd rather -- could you add this variable? Or divide these two things? Yeah, we can, kind of, make that work -- or it comes from our partners. Can you make it run faster? Make the output look better, so it's easier for them. Sometimes it comes from our analysts, and say if we change this a little bit, it would make my life easier and we'll modify tools along the way. There's actually modifications going on pretty regularly.

Then there's really new features. As Azadeh mentioned, the work that FDA has done in methods work. So that's -- think of new feature being -- adding a new method. A self-controlled risk interval now exists in Sentinel. It didn't exist two years ago, so now there's a feature. It's a tool that you can do. That's the idea of these new analytic capabilities.

Query fulfillment. Every time FDA asks the question, we have a very standard way of answering it. FDA will send us a construct -- this is for the rapid kinds of queries. They'll send us a brief question. If your question is in English, we do a little triage. Can we answer it in the system? Then there's a stage where we're going through specifications -- specification development and review. Once we find -- finish that, we send it to our partners. They send the results back. We put the reports together and hand them over to FDA. That cycle -- that query fulfillment cycle is -- I skipped this slide, but it goes through all these steps when we answer it. These steps you can do in a day or two, or it takes a month. It takes as long as it takes for the answers -- the epi answers to be specified -- but then once those are done, you can go pretty quickly. That's the idea. But the reason we have all those steps is to make sure that when we get those results back, it really is what you've asked.

I'll finish with what the future looks like, and this is a little bit bigger. This is Sentinel -- the kinds of things we're working on, and this is Sentinel and PRISM together. What do we do when we think about expanding sources? It's new data sources. We're actually working with Kaiser Permanente to bring in some more inpatient data. We have some inpatient data through Hospital Corporation of America. We're going to work with Kaiser to bring in some new inpatient data. We are working in getting Medicare data into the Sentinel common data model so we can query the Medicare data in the same way we do our other partners. We can expand the data model. Two years ago, we didn't have patient zip code, now we do. All right, that's just another variable on a table, but that's the idea of expanding of new information -- but not new data sources. Then you expand analytic capabilities, and one of the ones we're focusing on -- we're always working on new methods, and now we're spending a lot of time -- and CBER has asked us to spend a lot of

time thinking about access to more timely data. That's really where we're pushing the -- trying to push the envelope now. It's can we get data that we're two weeks old, or three weeks old -- and we can. It's just figuring out how to best to do that within the constraints of the system and to meet the needs of FDA. I'll end there. Thank you very much. (Applause)

DR. OBIDI: I would like to thank our presenters. Right now, we're going to take some questions from the audience. I'd like you all to keep in mind that we do have people listening online, so if you have a question, please state your name. Then for the people listening online, just put your question in the text box and we'll have someone here read your question. If anyone has any questions, we can start. Oh, just press the mic button.

DR. LONGSTRETH: Janice Longstreth, Emergent Biosolutions. What percentage of (NOISE) -- oh, sorry. What percentage of the health care records do your providers cover, do you think? Or the insurance claim records?

DR. BROWN: So I'm not sure I understand the question. Let me try to answer it and I'll see if I did.

DR. LONGSTRETH: (Laughs)

DR. BROWN: The -- we expect our partners -- our data partners will have complete longitudinal information for their members between their enrollment start and enrollment end. If you're a member of a health plan from that start date to end date, we expect to see all medically attended events -- or maybe even said it differently. It's things that the plan's paid for, so we won't see things like an outpatient -- sorry, over-the-counter medication. Won't see vitamins, but we will see things that are billed for essentially.

DR. LONGSTRETH: Yep, my question wasn't clear. I was actually asking what percentage of the US population do your data partners cover?

DR. BROWN: I won't do the math in my head. It's a -- it's a -- I should just not do the math in my head. I'm trying to think of the -- the US population is, I think there's a hundred and some million people are privately insured. I'm looking at Kevin to see if I get a nod. It might be about a hundred and fifty million privately insured in the country, and there's probably about 40 million current members.

DR. LONGSTRETH: Do you have any idea of representativeness?

DR. BROWN: Well, there are privately insured, so we won't have good

representativeness for Medicaid. We won't see Medicaid. The older population's under represented because of Medicare --

DR. LONGSTRETH: Yeah.

DR. BROWN: -- although we're bringing Medicare in now, and we're certainly missing the uninsured, but there's fewer and fewer uninsured. Across the country, it's a nice representation. Our big national insurers are national, so they have representation in most states -- or together they represent most states.

DR. LONGSTRETH: Thank you.

DR. ROCKHOLD: Frank Rockhold from Duke. I have a question that's based on -- somewhat on experience, now maybe it'll be covered later -- where I spent a lot of time working with the Core Nets to face some of the similar kinds of issues. When you -- obviously the coding mechanism at an individual site is tied to their local medical culture, or billing system and that obviously drives what goes into the database. So when you -- when you get -- it was a great presentation by the way. It's one of the best presentations I've seen in Sentinel, so thank you. When you get these individual outputs from the individual sites, what do you with the heterogeneity that you know is inherent in the question around the event that you're trying to estimate? Do you account for that? Do you try to adjudicate it? And if that maybe more relevant to the Tree Scan discussion, I don't know, but I'd just be interested in your views on that.

DR. BROWN: Sure, so thanks for the comments. The -- so you're exactly right. The -- these partners are -- when you think about how the data feed up through the system. You go to a doc, it gets into electronic medical record, then it goes to a billing system, and then a bill is submitted and everything that happened may or may not be on that bill. Different kinds of claims will have different levels of confidence for us, so inpatient data are always audited. Outpatient pharmacy data are always audited. Outpatient procedure data are always audited. Outpatient diagnosis are not. We know these things, so we try to use that knowledge to develop the specification, so we're not trying to get more out of the data then they can really tell you. How do we do some of those things? Lots of sensitivity analysis. What if we defined it -- the outcome -- three different ways? Using inpatient and emergency department, or just inpatient data to try to see if it makes a difference. We do a fair amount of that kind of work. We will always compare the data when it comes back from the partners -- we will always compare data across the partners when they come back to try to identify variation. Then I think later today, we'll see some of the methods we might use to do that -- so statistical methods to do it. But what's actually nice is because we have multiple partners, we can compare them. There's -- we

hadn't -- this was a nice -- an added benefit. If you're using one database, you see the numbers. You don't quite know what to think about it, but if I have four national partners, I wouldn't expect there to be a lot of big differences if it's controlled by age or sex, once you control for that. Should I really see a lot of variation? If I do, I'll ask a question. It's actually been a benefit for the research, as well.

DR. ROCKHOLD: No, no, I agree. Thank you. I mean, the heterogeneity isn't a bad thing. It actually can be -- it can be informative. It might be an issue for FDA, but I'll ask that question later.

DR. OBIDI: We're going to take -- we're going to take one more question just so that we can keep the schedule on track.

DR STRAUSS: Thanks. Walter Straus with Merck Research Laboratories. Sentinel was based upon administer of claims data as the infrastructure, and since the inception of Sentinel as a consequence of the High Tech Act, there has been a rapid upscaling of the use of electronic medical records which obviously have some significant advantages. I'm just wondering in terms of the future of Sentinel, what the intent is in terms of capturing more EMR- based records relative to the claims framework that's been so well established?

DR. BROWN: Yeah, so thanks for bringing that up. Your -- we spend a lot of time now thinking about how to -- how to get value out of those EHRs. The country has spent so much money to put essentially everywhere now, so the EHR data will be rich in clinical detail but lack the longitudinal availability. The most valuable source would be linking the two together -- linking the two brings up all sorts of other problems of how do you do the linkage, and you're linking small populations. We're spending a lot of time trying to think through how to do it. I will mention that one of our new data partners, the Hospital Corporation of America is one of our new partners. It's a -- they have up to 160 hospitals across the country and that is an EHR system. It's a sole -- it's a stand-alone -- we think of it as a stand-alone EHR system and CBER's been using that to look at blood products because it can't get at blood products any other way. Inpatient medications we're blinded to in the claim, but we can get there. We're spending a lot of time trying to think about how to make use of those data in a way that makes sense, right? It's got to answer that question, and we have pockets within Sentinel that have those, but it's relatively small pockets -- but (inaudible) and Sentinel have actually been thinking a lot about -- they've been doing some linkage projects together. Actually just starting two linkage projects between Sentinel partners and the Core Net partners to see how we might get those data to work together. Because that's really the big value -- if I could get them together. So that's the challenge, but that's where the -- that's the real goal.

DR. OBIDI: Okay. Thank you, everyone. We're going to start Session III.

Session III: How has CBER been using PRISM? Signal Refinement and Evaluation

DR. ZINDERMAN: Hi, good morning. My name is Craig Zinderman. I'm the Associate Director for product safety in the Division of Epidemiology and OBE in CBER. The next session is about how has CBER been using PRISM. Our first speaker is Dr. Meghan Baker. Dr. Baker is the Assistant Professor in the Department of Population Medicine at Harvard Medical School in the Harvard Pilgrim Health Care Institute. She's going to be talking about signal refinement and evaluation.

Signal Refinement and Evaluation

DR. BAKER: Thank you very much, and thank you for organizing this exciting meeting. We appreciate being here. I'll be opening Session III and really focusing on signal refinement and signal evaluation. I have no conflicts of interest.

When we think about post-market safety surveillance, we can think about three stages. Signal detection, where we identify unanticipated adverse events. Signal refinement, the initial evaluation of potential safety concerns that may have risen during product development or after licensure, and there may be through medical risks based on commonalities among products, so the same class or containing similar product components. We can also think about safety evaluation which is formal assessment of potential safety concerns.

In Sentinel, we've been using Sentinel data mining methods to address signal detection. We often consider Sentinel reusable and customizable tools to address signal refinement. For signal evaluation, we've traditionally used protocol-based assessments. I want to note that other systems and activities also address post-market safety surveillance and these include FAERS or VAERS for passive surveillance. Other examples of systems or activities that address signal refinement and evaluation include vaccine safety data link, and a clinical immunization safety assessment project, as well as risk evaluation and mitigation strategies among other assessments.

We'll hear more about Tree Scan this afternoon, but Tree Scan is a data-mining method that implements a tree-based scan statistic. This can be used to simultaneously evaluate hundreds or thousands of potential adverse events, or groups of adverse events to determine if any of them occur with a higher probability among patients who are exposed to a particular vaccine, and it adjusts for multiple testing.

Signal refinement then often comprise either a rapid one-time assessment of accumulated evidence of a product, or a perspective repeated sequential monitoring of data as it accumulates over time. The emphasis of -- the emphasis of signal refinement is really on the speed, and we often consider the use of reusable and customizable tools when possible.

Signal evaluation then continues the work of signal refinement. It focuses on setting a

safety concern or whether or not association exists and is likely to be causal. It often requires a protocol that's tailored to the specific concern and it often requires chart review but not always.

If we take Gardasil 9 as an example, it was approved by FDA in December of 2014. We plan to use Tree Scan for signal detection to identify unanticipated adverse events among females and males between the ages of 9 and 26. We also -- we also plan to use customizable tools to address prespecified potential adverse events for signal refinement, and in this specific situation, we plan to use sequential methods. Then finally, if there's a potential safety concern, we have the ability than to create a protocol tailored to address that specific safety concern and signal evaluation.

Advantages of the customizable, reusable tools include the fact that we have very rapid access to population-based data -- and I know we heard quite a bit of that from Jeff earlier today. There are flexible parameters and we've been able to find simple adjusted incidence rate ratios.

Disadvantages of our customizable tools include the fact that we're dependent on the accuracy of electronic codes, and that we can only distinguish among products with those distinct codes.

We had limited ability to control for confounding, but I would say that's changing as the tools become more and more sophisticated. Now we have increased ability to control for confounding and to complete sophisticated analysis using those tools. For example, we can think of a propensity score analysis and we can use the cohort identification and descriptive analysis tool to identify the exposure and compare the cohorts, extract covert information. Then we can estimate an exposure propensity score and match the exposed and compare our patients on the propensity score. This is one way that we can think about control for confounding.

I would say this is the original slide where we looked at the three stages of post-market safety surveillance. I would say now we can consider also using our reusable and customizable analytic tools for signal evaluation in certain situations, and as we develop more and more sophisticated tools.

Then when do we need to do a protocol-based assessment? I would say for right now when a reusable analytic tool is not available for the specific analysis required, or when the outcome algorithm is too complicated for the current tools that we have. Also if maximum control for confounding is needed, we might consider a protocol- based assessment, and also if we want to integrate additional data such as immunization registries or birth registries.

We can perform chart review when it's deemed necessary, and that might be for signal evaluation or even for signal refinement. We usually use this for protocol- based assessments, but it's not limited to the protocol- based assessments. We can request for test records to confirm specific exposures or outcomes. The -- we use this usually when the exposure's incompletely captured in administrative data, or if electronic algorithms are

really not perfect at identifying cases of the outcome.
I also want to mention that we have the ability -- when necessary -- to look at a claims profile listing of all electronic claims for a prespecified period, and we've called this PEPR, patient episode profile retrieval. This is a limited de-identified patient level case data. We don't use that to validate an outcome, but rather to determine whether we need to investigate it further.
You saw this slide in Jeff's slide deck, but the question often comes -- how quickly can we complete a typical analysis? If we use a customizable tools, it can be in days to weeks -- those are the modular programs. Very -- the time that's spent on this is often on the specifications and really creating the question and making sure that we have the appropriate specifications. If we use those tools and then add a custom program to that, that can add to weeks to months, and it allows us to have more analytical flexibility, and also build on the tools that we have.
Finally, when we think about a protocol-based assessment or analysis, we think of months to years and this is because of the protocol development, as well as the programming. Then often, we'll include chart review which can add months to the -- to the assessment. I wanted to thank the Sentinel Operations Center, FDA, CBER, and our Sentinel collaborators and data partners. Then we'll turn it to the next speaker. This is an extra slide. (Applause)

DR. ZINDERMAN: Our next speaker is Dr. Katherine Yih. Dr. Yih is an epidemiologist from Harvard Pilgrim Health Care Institute and she'll be talking at -- or she'll be giving some case examples where we've used PRISM.

Case Examples of PRISM Utility

DR. YIH: Thank you. Good morning, everyone. Well, there's a lot of clickers here. Let's see if I get the right one. As Craig said, I'll be talking about some cases examples of our evaluation of vaccine safety signals. I have no conflicts of interest.
I wanted to start with some considerations to bear in mind in studying vaccine safety. It's, kind of, simple- minded, but generally vaccines are given to healthy people, often children, whereas drugs are generally given to sick people who are undergoing treatment, and so the tolerance of risk is much lower for vaccines than for drugs. As Dr. Mark said earlier this morning, there's -- there are movements of people who are skeptical about vaccines or hesitant to get their kids vaccinated. This has been going on for at least a couple of decades, and it poses a threat to public health as, I think was illustrated quite nicely, by the measles outbreak we had nationwide a couple of years ago. It's essential to have vaccine safety monitoring in place. It's also really crucial to implement careful control for confounding. I mean, this is a case for any epidemiologic study, but it -- I guess they would argue that it's even more important for vaccine safety studies because it's really -- we really, really want to avoid spurious findings in either direction. Either finding a risk

when later turns out not to be the case, or the other way, where we do a study, we find there's no risk and -- no increased risk and then later turns out that there is. Because these kinds of things can lead to a loss of confidence in immunization -- the national immunization program, the recommendations of the national committees on immunization practices.

Also, I would throw in here that to, sort of, maintain the credibility of results coming out of vaccine safety studies, in our experience it's really been very important to do chart validation of the outcomes because these electronic algorithms -- or the algorithms that are -- that we use to detect potential cases aren't perfect, and so they'll detect things that turn out not to real cases. We often end up doing chart review which is very time-consuming in our system.

I've, kind of, answered, I think in a way my question here of why do a protocol-based assessment. It's really a way to allow us to have a very customized approach for a specific study question -- an approach that allows us to do careful control for confounding. As Meghan mentioned, we do have tools that are -- that we have in -- that we use in Sentinel, but sometimes they -- they're not perfect in controlling for all the potential confounding -- confounders in a particular association that we're studying.

I will talk about three protocol-based assessments we did about some vaccines using the PRISM system. They're listed here, but I'll be going through them, so I won't pause longer here. I've, kind of, color-coded them, so the rotavirus vaccinations and intussusception is in green. I think folks here are quite familiar with this -- with this vaccine outcome pair, so I won't go into talking about intussusception.

Some background is that there was an earlier rotavirus vaccine called Rota Shield which was licensed in the late 90s. It was withdrawn from the market within less than a year due to the observation that it was an associate -- that it was associated with an increased risk of intussusception. The magnitude of the risk was estimated to be on the order of one to two excess cases per 10,000 people vaccinated -- infants. Then there were these two newer vaccines that are now in use, RotaTeq and Rotarix. Those underwent larger than usual clinical trials in order to be able to detect an excess risk of intussusception of the magnitude seen for Rota Shield, if indeed such a risk existed. The clinical trials for each of those consisted of more than 60,000 infants. No increased risk was seen during those clinical trials. The vaccines were licensed in the years shown in parentheses here. But then, after the vaccines started being used in this country and elsewhere, there were -- there were results that came to light suggesting that there was an increased risk of intussusception associated with both of those vaccines.

This PRISM study was launched in order to determine the risk in U.S. infants, and of course, the vaccine safety data link also had been doing studies of both of these vaccines so that the evidence from those studies were very much part of the whole that was, kind of, available to the immunization authorities in this country to, kind of, consider.

In terms of the design, our primary design was a self-controlled risk interval design. This

uses vaccinated infants -- vaccinated cases really only -- and it's very nice, and we -- you'll see that in other examples, we use this design also. We like it because it -- it's -- it controls very well for fixed risk factors. Things whose -- that don't change over the course of the risk and the -- and the comparison window. For example, sex, race, social economic status.

We use two risk intervals for this study. The first week after vaccination, and the first three weeks after vaccination based on results from other studies and biologic plausibility. We also use temporal scan statistics to look for clustering of cases in certain temporal periods after vaccination, and the challenge in this study was to deal with the confounder of age. This graph in the lower right was taken from a paper by Jacqueline Tate and the x- axis is the first year of life only, and you can see that the background incidents of intussusception hospitalizations varies drastically over the first year of life, peaking at about six months. Of course, rotavirus vaccination is associated with age also because there are recommended ages for vaccination at one -- at two, four, and in the case of RotaTeq, six months of age. This was -- would have been a very strong confounder, so we explicitly controlled for it.

I'm going to present the results for RotaTeq. The Rotarix results were very much in the same direction, but there were only about a tenth as many doses which is really the case for the U.S. population as a whole. We had much less precise risk estimate, so I'm concentrating on RotaTeq here. We had more than half a million first doses of RotaTeq in our -- in our data, and more than 1.2 million total doses. We found that the first dose was associated with an increased risk of intussusception for both of the risk windows. We, also, using the temporal scan statistics found a statistically significant cluster on days three to seven after vaccination, and this histogram here shows the - - for the all doses, it just shows you this, kind of, clumping of the cases there on days three to seven.

We had a -- we did a number of primary -- we had a -- also a secondary study design and we had primary and secondary analysis -- and all the attributable point -- risk point estimates were in the range of 1.1 to 1.5 excess cases of intussusception per hundred thousand first doses, so this was approximately 1/10 of the risk associated with -- at earlier vaccine of Rota Shield vaccine. It did not lead the Advisory Committee on Immunization Practices to recommend any changes to vaccination policy with respect to rotavirus vaccination because the risk was deemed to be -- the benefit was deemed to outweigh this level of risk. However, it did lead to a change -- it -- some action on the part of the FDA. The FDA put out a safety communication based on the study in June of 2013 pointing out that the label of the RotaTeq vaccine had changed, or was changing. Here's the top of the label. It mentions intussusception on the left here, and then in the warnings and precautions, the study is mentioned referring to a couple of sections later in the label -- 5.3 and 6.2 which are shown here. So 5.3 discusses very briefly the results and the finding of this increased risk, and here's the section 6.2 which goes into somewhat more detail about it. That was -- that was the outcome of the -- of this study regarding the -- with respect to FDA

action.
The second example is the 2010-11 Trivalent inactivated influenza vaccine and febrile seizures, and this is among children less than five years of age. The reason this was undertaken -- the study was undertaken is that there was a signal from VAERS. There had been disproportional reporting of febrile seizures after Fluzone and the FDA put out a notice of the VAERS finding on its website in the middle of that flu season. There was also a signal from the vaccine safety data link which had been doing sequential analysis, and so signals emerged and that - - they -- this was followed up by a fairly in-depth investigation by my colleague, Alison Kawai, who was then Alison Tse. In her study -- or in the VSD study, it was found that the flu vaccine of that year and the pneumococcal conjugate vaccine were each associated with an increased risk of febrile seizures. Furthermore, it was found that the -- or there was a suggestion of a greater risk of febrile seizures if a child got both of those vaccines on the same day, compared to getting them on separate days. The preliminary findings were reported to the Advisory Committee on Immunization Practices during the season. The vaccine information statement that's handed out to parents bringing their kids in for vaccination was updated to include a statement of the apparent increased risk with that same day vaccination -- with the flu vaccine and pneumococcal conjugate vaccine.
Here -- also we use the self-controlled risk interval design. In this case, the risk interval was days zero to one -- that's the risk interval that seems to be appropriate for seizures. In this case, we also had to worry about confounding by age since -- for the same reasons that we did in the case of rotavirus and intussusception, but also sees anility since febrile seizures can occur when a child has a fever, and there's many diseases whose incidents changes by season who -- that brings fever, and therefore, increase the risk of febrile seizures. Furthermore, there were concomitant vaccines to worry about in this case. We didn't worry about them in the rotavirus case because it's an oral vaccine. It's the only oral vaccine and the outcome was a good outcome and it didn't seem plausible that intussusception would be related to injected vaccines. But here we do have to worry about them because of so many vaccines being given to infants at two, four -- at these ages that the flu vaccine is given.
We explicitly adjusted for age, and for calendar time, and also adjusted for two concomitant vaccines. We had more than 600,000 flu doses. We found there was no statistically significant increase in risk observed. However, the authors did point out that the point estimates were somewhat elevated even if it wasn't a statistically significant increase in risk, and they went on to calculate the magnitude of the -- of the risk and found that it was -- it was lower than originally thought, so that allowed some reassurance to be given. Also, the study found that if kids received same-day vaccination of the flu vaccine and the pneumococcal conjugate vaccine, that they were not at significantly increased risk of febrile seizures, compared to getting those two vaccines on separate days.
Since this was technically a null result, the FDA put out a communication and said that

it -- just announcing the results of the study and saying that they were not requesting any changes to the prescribing information for Fluzone or any of the other influenza vaccines. Fluzone is the one most often given in that age group, or in the -- in the younger children that is.

The third example is the human papilloma virus vaccine, the quadrivalent one -- Gardasil and venous thromboembolism. The reason this study was taken up was, that there were signals from both VAERS, as well as VSD. Although the VSD signal was not statistically significant, but nonetheless, the point estimate was somewhat elevated. In both of those cases -- the large majority of the cases had another -- at least one other risk factor for VTE, so it wasn't really, sort of -- there wasn't a -- sort of a clear concern that the vaccine was associated, but nonetheless, there was enough of a concern that the FDA's Pediatric Advisory Committee requested the PRISM study. Here again, we used the self-controlled risk interval design and a four week long risk interval starting the day after vaccination. We use temporal scans statistics again, as in the case of rotavirus, and here the confounder of concern was duration of combined hormonal contraceptive use which -- and so, this graph is from a different study by Vlieg et al, and it shows you that in the three months after starting oral contraceptive use or combined hormone contraceptive use, the risk of venous thromboembolism is elevated, and it goes down with the time on contraceptives but it never goes down to before one starts. So we needed to explicitly control for that, which we did.

We had 1.4 million total doses and we found no evidence of an increased risk of venous thromboembolism after Gardasil in -- from either the self-controlled risk interval analysis, or the temporal scan analysis and this is the histogram. The colors just represent different dose numbers of the HPV vaccine with no clear cluster. This also lead to the FDA putting out a safety communication pointing out that other studies also found a null result, and ours agreed with that, and the FDA was not requesting any changes to the labelling. This is -- my time is up and this is my summary slide. Just putting the study side by side showing some of the features of them. I'll end just with saying that we did also publish -- we, of course, did our final reports for FDA, and we also published the papers in the scientific literature. Thank you very much. (Applause)

Integration of PRISM into Regulatory Processes

DR. ZINDERMAN: Okay, thank you. By moving right along, it's me again. Going to talk about how we have been, or could be using PRISM in CBER's pharmaco-vigilance work. I'm going to describe to you our routine, or day-to-day safety monitoring activities in CBER to evaluate the safety of CBER license vaccines and other products. I'll also discuss some of the work products that we are required to do and have integrated as part of our safety monitoring process. These include some communications, and safety evaluations, and reports. Then finally, I'll give some perspective on where we've been using PRISM or where we could potentially use PRISM as part of each of these processes.

I'm sorry -- much of the post-marketing surveillance work that's conducted at CBER is done in the Office of Biostatistics and Epidemiology, specifically in the division of epi which is staffed by medical officers from a broad range of disciplines, as well as PhD level epidemiologists. We can think of our day-to-day work in three different categories. The first is the preapproval of pharmaco-vigilance review. While most of our work is in the post-market setting, we do began in the preapproval phase. Prior to licensure at the end of Phase 3 when products -- company sponsors are applying for approvals -- FDA approvals of their product, we assess the potential safety and concerns that have been identified at that point, and review the pharmaco-vigilance plan which is a company's plan for how the safety of the product will be monitored after approval. Second, medical officers and epidemiologists conduct ongoing review of spontaneously reported adverse events to the vaccine adverse event reporting system, or VAERS, that Dr. Shoaibi was talking about earlier. You might call this our traditional pharmaco-vigilance work, and it includes review of selected incoming reports as they're received by FDA and CDC. But we also do periodic analysis, of course, of the accumulated safety data from these reports. Last, pharmacoepi studies that are conducted by CBER, or by CBER staff participating in the studies.

That first category was the preapproval of pharmaco-vigilance review.

Pharmaco-vigilance reviewer is assigned to the interdisciplinary review committees. They're assigned with assessing sponsors applications for approval of a new product. The objective of pharmaco- vigilance review is start planning early for the monitoring of safety after licensure, and having an adequate plan in place as soon as the product's licensed. All BLAs are expected to have pharmaco-vigilance plan submitted with the PVP. The International Conference on Harmonization, or ICH, has a guidance -- the E2E pharmaco-vigilance planning guidance that gives information on the expected content and structure of a pharmaco-vigilance plan. The PVP reviewer is evaluating -- if the sponsors have adequately identified any possible safety concerns that might be associated with their product -- and they're doing that based on data that's presented in the PVP by the sponsor and -- which is mostly safety issues that have been identified from the clinical trials that have been conducted as part of the products development plan. I'm going to also -- based on the reviewer and FDA's own experience with that product, perhaps in prior marketing for other indications, or similar products that have already been marketed either in this country or abroad.

The Phase 4 studies are planned that the pharmaco- vigilance reviewer evaluates the methods, the size, potential confounding, and other design characteristics of any plan studies and provides recommendations for improvement. The review committee also considers if post- market safety studies should be conducted, and to further evaluate any potential safety issues that have been identified to bolster the already accumulated safety database. They also had to consider if those studies should be implemented as PMRs, post-market requirements under FDA authority to require safety studies to be done, or if

risk evaluation and mitigation strategies, or REMs, need to be conducted to ensure safe use of the product.

PRISM has become a part of this pharmaco-vigilance review. For one, results have completed PRISM studies on similar products can complement that accumulated safety database on which you're deciding how you're going to monitor safety -- pharmaco-vigilance -- and how you're going to conduct pharmaco-vigilance post licensure. It's going to affect, you know, what's your assessment of the safety concerns that are potentially associated with that product. When the pre-license reviewer includes potential safety concerns that warrant additional surveillance activities beyond routine spontaneous adverse event reporting, FDA and the sponsor have to consider what activities are necessary. PRISM can be an option for conducting a study to further evaluate those safety issues like some of the examples that you heard previously. PRISM or some components of PRISM could also potentially be an option in other capacities like the rapid base queries or other studies that I'll talk about in -- a little bit more.

While safety databases for vaccines typically have numbers of subjects in the thousands -- we saw 60,000 subjects in the rotavirus studies -- the extent and breadth of exposure that can be assessed in clinical trials is often, at least somewhat limited, for most products and has certain limitations. Even in the absence of a safety concern that warrants an additional study to evaluate a specific safety issue, PRISM is a potential source of conducting additional studies on the safety of a product in a more broad manner without specifying perhaps a single outcome, but a number of outcomes that are of interest for that product or that category of products. You might call the general safety studies, and Dr. Baker gave an example with Gardasil-9, if -- you know, we intend to conduct that for a sample of outcomes. That, sort of, general safety study can augment the preapproval safety database because now you're studying at post-market with a much larger patient population than in the clinical trials and a much -- a wider variety of patients in terms of demographics, concomitant use, concomitant vaccinations. It's a more real-use experience than perhaps was done in the clinical trials.

Then last, future signal detection activities. I think everyone's mentioned this idea of Tree Scan and this data-mining activity of looking for safety signals using the breadth of the PRISM, or the -- or the claims data as opposed to focusing on a single outcome and further evaluating that outcome, but using this Tree Scan methodology to identify signals. That can be part of the pharmaco-vigilance plan that FDA or even sponsor has for a product to further look for new safety signals after licensure.

The second category that I mentioned of our work in our routine pharmaco-vigilance monitoring is our, of course, post-market spontaneous adverse event surveillance. Report of adverse events can reported VAERS from providers, patients, consumers, really pretty much anyone. VAERS is co-administered by FDA and CDC, and there's a contractor that receives the reports, processes the data into the database, and assigns MedDRA codes to what's been reported. The reports themselves, particularly from the healthcare providers,

consumers and patients just -- is mostly a free text format as you'll see on the form. They have to be coded into a standardized terminology. The VAERS contractor also conducts follow up for a certain serious reports. They'll contact clinicians involved in the case, or patients, or parents sometimes and get additional medical records and information on the outcome of that case and the circumstances of the adverse event. They have received over 30,000 reports annually, about 20 percent are serious. There's general indication of, kind of, a lot of the non- serious things that we see after vaccination, or that are common in children -- in -- you know, in general, like rashes and fevers. About 40 percent of the reports to the databases is from manufacturers, so there's a substantial amount of reporting directly to the VAERS database from patients and providers.

This is the VAERS form and collects pretty much what you'd expect it to collect. There's information on the patient that's collected that received the vaccination. And there's information on who administered the vaccine, the kind of adverse events that they had, demographics like age and gender. The seriousness of the adverse event, when the vaccine was administered, when the adverse event started. Then, of course, which vaccines were administered and how were they given.

At CBER, we have a pretty standardized process for how we review these adverse events. The medical officers that I described earlier, and epidemiologists, are each assigned a panel of vaccines, so they get familiar with those vaccines that are in their panel and we try to keep those pretty consistent over time. Each staff member is responsible for reviewing the serious adverse events that are reported to VAERS as they come in. Actually, at this point, individually reviewing them, or most of them in an almost real-time basis. Also conducting aggregate review of the adverse event data that's been accumulated for each product on a periodic basis. When we look at this adverse event data, of course, we're counting trends and the most important things that we count, of course, is the frequency of the -- of which adverse events have been reported. What are the common ones, and what kinds of -- and types of reactions are we seeing for each product in these reports. But we also look at U.S. versus foreign, gender and demographics, and we compare that to some historical period, like some five years or a certain number of year period in the past to see if anything's new with that vaccine.

There's also a literature review conducted, analysts -- so data-mining analysis. In this context, the data-mining analysis is disproportionate analysis where we're comparing the number of adverse events that have been reported for that vaccine to see if it's more frequent than the frequency that that adverse event is reported for all other vaccines.

Spontaneous adverse event surveillance has some advantages and disadvantages. It's conducted in almost real-time so we can -- a medical officer will be receiving and reading a report, you know, sometimes within days, or at least a week or two after the person submitted it, and written it out and submitted it. It can be relatively quick. That's relatively inexpensive compared to conducting a clinical trial anyway. Since, like you saw that form, is open-ended, you can pretty much report anything you want. It's good for

detecting unexpected safety signals. We're not prespecifying anything here. You can put whatever you want, and MedDRA is extremely is granular and extremely large, so anything will pretty much corresponds to some kind of fairly specific MedDRA term. But there's limitations. There's underreporting and that's the most important thing, right. Most people aren't going to take the time to fill out and submit a report, so we only hear about really what we call, the tip of the iceberg. We don't know the full denominator, how many people are really getting exposed to that vaccine. Reporting, since it's spontaneous or passive, is subject to a lot of biases, particularly stimulated reporting. So when you see media announcements, like at the time that Rota Shield vaccine was pulled off the market in 1999, there was lots of press and then there were lots of VAERS reports about intussusception. The quality reports -- it's a blank form. You can fill out all of it. You can fill some of it. You can fill out a couple fields. It all gets submitted, so sometimes there's a lot of missing information. Of course, we have no unvaccinated comparators. We know whose reporting some adverse events to us. We know how many reports we've got, but we don't know if those events would be occurring at the same frequency, or even more frequently in a group of people who were not vaccinated at all. It's only a vaccinated group that we're seeing.

When we look at PRISM and how it's involved in adverse event surveillance, VAERS is not the only source of post-market surveillance data, of course. There could be post-market studies that are conducted by the company, or conducted individually by other institutions. We could also get information from literature, as I mentioned that's part of our process -- or foreign regulators might detect, or have additional information and we communicate with them regularly. We generally think of these sources as contributing to signal detection, right. We're looking at adverse events, and we're generating hypotheses about, you know, what are new potentially adverse events, or potentially associated with these vaccines. When we think about PRISM's role, we're usually thinking about using PRISM to conduct a formal study, like the protocol-based assessments that you just heard about. We're evaluating -- or validating a potential vaccine adverse event association and we're either confirming that it is truly associated, or perhaps we're not finding a signal, like in a couple of the last two cases. We're not finding something and we're, you know, in essence rejecting -- or at least not confirming a signal.

But we can also use PRISM in other ways, and we heard earlier about some of those automated query tools or modular programs that can complement traditional pharmaco- vigilance by giving us an expanded capacity to look at the kinds of populations that are experiencing any adverse event, perhaps, and do some limited comparisons between vaccinated, unvaccinated cohorts, or vaccinated time to unvaccinated time in the case of a self-controlled risk interval. We can further assess some potential vaccine adverse event associations, even if we don't have a more robust, definitive answer, like the kind of thing that we would do in a protocol-based assessment in getting a lot of information. Then last, the signal detection methods and we've already talked about that.

So that fits on the higher part of this further -- the top part of the spectrum as it's displayed here and in signal detection portion of the spectrum.
I said I would talk about a couple of other work products. One of those is pediatric safety reviews that we conduct for the Pediatric Advisory Committee, so FDA is required to present a summary or an analysis of pediatric safety of all products, 18 months after approval -- after all new approvals that have involved some pediatric indication. We haven't routinely used PRISM as part of this presentation to the pack, but it is an option on as we go forward to further evaluate safety concerns, and notably, when we have an issue that is associated with a product or a product class, again, in the context of discussing that with the pack and presenting those results to PRISM, we can potentially further evaluate the pediatric population using PRISM.
Last, there are Section 915 evaluations, and this is another one of these routine processes that we're required to conduct, where we do a summary analysis of adverse events for all products -- 18 months after approval and use in 10,000 patients. We can use PRISM as part of that, since this is really a signal detection activity. Since it's being done for new products, it makes sense to fit the Tree Scan portion of that in here, and potentially use Tree Scan as a routine part of this, sort of, new product safety evaluation.
Last is PRISM and pharmacoepi studies, and of course, PRISM is the primary CBER tool for pharmacoepi studies in the vaccine area, and it complements Medicare data which we also use separately outside of PRISM for influenza vaccine monitoring. And we coordinate with the vaccine safety data link at the CDC and some other speakers have already talked about that.
In summary, it can inform pharmaco-vigilance planning. It complements our, sort of, traditional adverse event surveillance, and we can deduct studies to refine or evaluate signals and also have the signal detection tools to potentially implement as we move forward. Thank you.
(Applause)

DR. ZINDERMAN: Does anybody have any questions about any of the three talks?

DR. DAVIS: I have a question. Bob Davis, University of Tennessee. Your talks were really quite good and presented a lot of information in a very concise manner. My question actually has to do with whether you've considered the use of some Bayesian methodologies to incorporate some of the past published data. For example, on the Gardasil study that you're planning -- not the one that you've completed, but the one that you're planning, there's considerable evidence that Gardasil is safe from a very large post-licensure state. That was done, I think in Southern California Kaiser. So there's already some pre- probabilities of what you'll find, and that might inform how you actually analyze your data in terms of evaluating potential false/positive signals that you get. Similarly, the study you had of the rotavirus vaccines showed lower confidence intervals of

0.8 and 0.9 throughout -- of mildly elevated relative risks, and I'm curious whether or not you considered adjusting those for the pre-likelihood that there was, in fact, a mildly elevated risk which might have actually made the risk you found statistically significant?

DR. YIH: Thank you very much. The short answer is, no, we did not. We did not use those methods and I don't remember discussion of using them, but I think it's something that we should discuss amongst -- among our research group for the studies coming up. Personally, I don't know how to implement those things, but we'll have some conversations and see. Thank you very much for the suggestion.

DR. SEIFERT: Hi, it's Harry Seifert from GSK. I'm going to ask you a vocabulary question that's going to evolve into a regulatory question. Sorry, Craig. I see the term signal refinement used, and it's been used probably for almost 10 years -- almost always in regard to Sentinel. But most of us who are in industry have to work globally, and globally we have the European pharmaco-vigilance regulations. There we don't have anything called signal refinement, but we have to talk about signal validation. I -- my first -- the first part of my loaded question will be -- my personal interpretation, which may not be the same as GSK's and I'm speaking only for myself, is that the two terms are generally synonymous. Would you like to comment on that? Or would you like to run screaming from the room?

DR. ZINDERMAN: Well, I'll speak first to it. I don't consider the two terms synonymous -- although this is somewhat semantics -- and we don't have an official, you know, regulatory action or classification that we assign to the word refinement versus the word validation. That might not be the case in the European regulations, but for FDA, we don't -- we don't assign a specific, you know, regulatory category. We're going to take an action in one category and not the other. But I do consider them different, and I consider them, sort of, on the spectrum that I think a couple of us presented. I think of signal evaluation as more of the signal validation where you're doing something that's definitive enough that you're going to make a decision -- you know, whether or not you need to take action or not -- and refinement is when you're developing a potential safety issue. You're learning more about it, maybe more about those populations. What do those patients have in common that experienced the adverse event? What are risk factors for that adverse event, maybe in terms of concomitant vaccinations or comorbid conditions. But you're not necessarily answering the question of whether there's a causal association or to what degree that association exists.

DR. SIEFERT: We'll negotiate that discussion offline.
DR. ZINDERMAN: (Laughs)

DR. SIEFERT: Then the second part is, sort of, my plea and it's, sort of, it'll come up again. But that is the plea that -- to the extent possible, realizing that they're different regulatory systems, I would hope that there's an eye towards global harmonization for a lot of -- as much as feasible and makes sense for a lot of the definitions but also responsibilities. I know Dr. Gruber's around and she's heard this from us more times than she wants to think about. So, thank you for that.

DR. ZINDERMAN: Thank you.

DR. SADDIER: I have a question. This is Patricia Saddier from Pharmacoepidemiology department at Merck Research Laboratories. The question may be for Katherine Yih. It's about chart validation, you mentioned the importance of that. I was wondering how that is actually performed in PRISM? And if -- like each partner does their own chart validation? And is -- there is a common protocol for that? A common definition that they all use? And also, if you have experience with non-acute events and the chart validation of non-acute events, like autoimmune disorders in a claims database?

DR. YIH: The way it's done is -- we have -- we develop chart abstraction forms, and chart extraction forms centrally with a lot, sort of, clinical expertise brought to bear. We sometimes compare with the obvious deforms and so forth. The data partners have their own vendors, so they -- to actually get that chart. So we identify the cases, and they look up addresses of the hospitals that the cases were seen at, and so forth, and seek the charts. Then -- actually, do a lot of redaction of the information that's too, you know, sensitive to send to us, and then we get pdf's of the actual charts. So it's all done centrally -- the actual getting extraction of the relevant data is done centrally. Almost always, or perhaps always, we have -- we have clinical adjudicators actually decide whether the cases conform to the prespecified case definition or not. It's not -- we don't have heterogeneity by data partner, you know, by virtue of them doing it by themselves. Regarding non-acute events, I'm thinking of whether we've used any of those outcomes. I mean, I think in terms of autoimmune, I would say this is probably an acute onset -- would be considered acute onset and that is the case of Guillain Barré syndrome. The other kinds of autoimmune outcomes we have -- as far as I remember, have not studied them using chart review yet. That is challenge. I think it will be a challenge when we do start to study those kinds of outcomes.

DR. OBIDI: I'd like to thank our presenters. We're actually going to take a 15 minute break now. One of the things I want you to keep in mind is no food, no drink. There is a café downstairs, so you're more than welcome to get coffee and there's a table outside if you want to place it there before coming back in. We're going to start the next session at 10:55. Thank you.

Session IV: Utilization of PRISM for Signal Detection-the future?

DR. FORSHEE: Hi, everyone. If you could please start taking your seats so we can go ahead and resume this next session on time.

Good morning, everyone. Welcome back after the break. My name is Rich Forshee; I'm the Associate Director for Research in the Office of Biostatistics and Epidemiology at the Center for Biologics Evaluation and Research. I've been involved in a number of Sentinel projects over the years.

In this session we're going to be talking about one of the newer initiatives that's trying to use Sentinel as a method for signal detection, and in particular, for situations in which we have not pre-specified adverse events that we might be concerned about, but we want to do a broader scan in order to see if there are any potential signals that may need further evaluation.

We're going to have two speakers followed by a panel discussion. The first speaker today is going to be Martin Kulldorff, who's done a lot of the work in the development of the TreeScan statistic that we'll be discussing during this session. Martin is a Professor and Biostatistician in the Division of Pharmacoepidemiology and Pharmacoeconomics s at Brigham and Women's Hospital and he is going to be discussing the TreeScan method that he has developed and that we have been testing in the Sentinel environment.

So, Martin, the floor is yours.

Signal Identification Method (TreeScan):

DR. KULLDORFF: Thank you, Richard, and thank you for inviting me here. It's a great pleasure to be at this PRISM work group day. So I'm going to talk to you about signal identification, and this is on behalf of the whole Sentinel TreeScan working group.

So the purpose here is how can we detect adverse reactions of the type that we didn't really expect to see. Well, we have -- we sampled with RotaTeq. There was a suspicion that maybe Intussusceptions will be problem because of the Rotashield vaccine that Kathy mentioned, but how do we detect things that we don't really even expect? And one reason for that, of course, is to detect problems that we didn't know about, but equally important is the opposite of the coin is we want to try to ensure that there are no (adverse reactions. And we can only ensure that by looking at everything.

So we can use a data-mining method, the TreeScan data-mining methods, and the goal here is to find -- so when we apply this to a vaccine if there are any known adverse reactions to this vaccine we want to find them because otherwise the method is not doing what it's supposed to do. And then we want to find any additional true adverse reactions, if they exist. We want to have few false positives, of if there are false positives, we want to find them that are easily explained, and then we want to have sufficient samples that will detect very rare adverse reactions, which means that we can say that if we don't find something then there's unlikely to be a problem there.

Now, when doing data-mining there are three key issues. One is the granularity, adjusting for multiple testing, and choice of comparison group. And I will a little bit about all of these three. So what's the level of granularity? Well, if we don't know what we're looking for we don't really know if you're looking for something very specific, like acute liver failure, or something of a like related diagnosis. And they give you two reasons for this. One is that it could be that a vaccine could cause a very specific problem, but it could also cause like more -- just like different problems with different people. But the other thing is that when physicians code things they might sometimes code it very specifically or they might -- different physicians might code it slightly different. Some might code a febrile seizure while another person codes a seizure.

So to address this (inaudible) we have a tree, a clinical diagnoses tree. So this is just a very small sample of that where we have in this case only five outcomes, heart attack, cardiac dysrhythmia, and cardiomyopathy, they're all part of the cardiovascular system. So they are on the same branch of the tree. And then we have kidney failure and kidney infections. They're both kidney problems so they're a separate branch of the tree.

Now at the lowest level we have about 6000 ICD-9 codes. And we removed some diagnoses, like accidents, (inaudible), that are unlikely to be due to a vaccine. We are looking for early onset adverse reactions, so we also removed cancer and other chronic diseases that could be caused by a vaccine, but it wouldn't show up within a few weeks. We also removed some very common mild conditions like fever that you will find in a clinical trial. So we don't need to have cross market surveillance for that. So this guy here to the right, for example, he's going to still be in the hospital, but it's because of the vaccine he took that morning, it's for some other reason.

So we use as a tree the multilevel clinical classification tree. And at the highest level, there are 18 big branches of the tree. If, for example, number seven, diseases of the circulatory system. And then at the second level we have hypertension and then we have diseases of the heart. And if we go down, at the third level we have, for example, peri-, endo- and myocarditis cardiomyopathy. And at the fourth level we have cardiomyopathy, and then the fourth level of the tree will have one more ICD-9 codes. So there's a total of five levels of the tree.

And then what the TreeScan statistic that is cut from the tree, so if we cut further down there we're eliminating is kidney failure. If we cut further up we say it's eliminating any type of kidney disease. Now, when we do this kind of surveillance we don't know what adverse reaction to

look for, what adverse events to look for, but also we don't know what the risk window is. If there is an adverse reaction, does it happen within a couple of days after the vaccination or maybe it happens to be four weeks after vaccine? We don't know. So what we do then is we combine the TreeScan statistic with the temporal scan statistic. A temporal scan statistic, what we have here, here we have over time. So at the left is the time of vaccination, and then we have seven adverse events from seven different people, and then

you want to see if any clusters of these events. And here is two and then it's zero, and then it's three, one, and one, so the definition of the temporal scan statistic is the maximum number of events in this window as it goes alone, in this case, three. And then we want to know well if there was no relation to the vaccine this would just be uniformly randomly distributed on this interval. So it was then the probability of having three in this window (inaudible) alone, is that something unusual or something that happens all the time probabilistically. And now we don't know the length of the time window either, so we drag several windows of different length around here and then we don't use counter number or events in the window, but we use maximum likelihood function instead to see what is usual probabilistically.

So we use a scanning window. We follow up these people for 56 days, 8 weeks, and then we have a scanning window that starts within 4 weeks of vaccination and that ends within weeks of vaccination, and is at least 2 days and at most 28 days, which gives a total of 665 potential risk windows that we evaluated.

As a comparison, what I'm presenting now is a self control version, so the comparison are those days in 1 to 56 that were not in the risk window. One can also use other types of comparisons with this TreeScan, but what I'm showing, you know, is a self control version. And then for each leaf, you notice a number of adverse events in each of the recent control windows, and for the higher level branches we have summed them up. And now we adjust for the multiple testing that -- TreeScan does that and it does that by taking the maximums in the following way: so the TreeScan, if you scan the tree by considering all possible cuts on any branch and all possible risk windows, so that's thousands and thousands, actually more than a million. For each counter risk window we calculate the likelihood and the cut window with the maximum likelihood, that's the most likely cut to the thing that's least likely to have occurred by chance, so that's our prime candidate for adverse reaction, but obviously we'll always find something with maximum, so the question is then is that so unusual that it would not have occurred by chance. And we have to adjust for this multiple testing of thousands of branches that handle the risk windows. So we generate 9999 replications of the data under the null, so under the null we know that's uniformly distributed over time and generate replications of that data set under a null hypothesis and then we compare the maximum likelihood from the real data set with the ones from the random data sets. And if it's among the five percent highest from real data set then that's significant at the five percent alpha level and the p-value is the rank divided by 10,000.

So I'm going to show you an example we did. This was a protocol based data- mining study for the HPV for Gardasil vaccine and it was posted on the FDA Sentinel websites. We were lucky we got some very nice comments from Merck. That was the only ones we got comments actually (laughter). I guess you can guess who is the manufacturer of Gardasil vaccine. We used a conditional three temporal scan statistic, which is self controlled. We had data from the four bit PRISM health insurance plans, and we have had

1.9 million doses, all first doses. So we used the first dose after the ninth birthday or enrollment, and both boys and girls. To define that an instant diagnosis, we don't want to include like repeat visits. If they have a condition and then they come back a few weeks, few months later for a follow up visit, we don't want to include that. So we only include a diagnosis for which there were not the same or similar diagnoses in the prior half year.
And this is the results for the HPV4 dose 1 analysis. So you should recognize here that we looked at 6000+ outcome definitions and these were the only ones that appeared at less than.05, adjusting for multiple testing. So the multiple testing adjustment is working very clearly here because if there was nothing in the data set we would have a 5 percent chance of finding one thing significant and a 95 percent chance this would be empty.
And you can see here that one of the signals, if you start from the bottom here, we have cellulitis and abscess of upper arm and forearm two to three days after vaccinations. There were 31 observed cases, which an attributable risk of 1.3 in 100,000, which is a very small p-value. So that's sort of a rash on the arm at the injection site, so that's a known adverse reaction to this vaccine. It's a very mild condition, so most people who get it would not go to the doctor, so it wouldn't be in our system, but at least 31 people did. You can see also that this cellulitis is part of the tree, it's part of the note 12, 12.01, and 12.01.01. Two of those are also statistically significant, but to a large extent are driven by the cellulitis. For example, 12.01 has attributable risk of 2.3, 1.3 of those are cellulitis. This is so the skin has 3.8 and 1.3 is cellulitis and 0.5 is unspecified erythematous condition, which I think another way to code a rash basically. So that was a known adverse reaction, so we were sort of happy that we found it because that means that we are able to find things that are things, but there's nothing that we were concerned about.
Another signal was the fourth level, 16.10.02.07, other complications of surgical and medical procedures, which is one to three days after vaccination with 36 observed cases, an attributable risk of 1.8 per 100,000. Also it's a very low p-value. If we sort of dissect at the fifth level, there were four post vaccination fever, seven other same reactions, eleven other same reactions due to vaccination, and 12 other unspecified complications of medical care. So obviously the post vaccination fever and other same reactions, those 15 were sort of -- the physicians thought it was due to the vaccine. But in the same reactions it doesn't say what it was that the vaccine caused. And what we did with this, using something called PEPR and TEVR, that Judy's going to explain, we looked into this and found that most of these were skin rash as well as a different way of coding it. Those were not skin rash were very few and all different, so there was no consistency in the remaining ones. So this is also known adverse reaction, but took a little bit more time to figure out, but we also did that.
So was this a success or a failure? Well, you could say it's a failure because we didn't find anything that we didn't know about. But that's good for vaccines, we don't want to find anything that we don't know about. We want to find that the vaccines are safe, so we were very excited about that the method worked well and found very rare things that are true, but

we were even more excited that it didn't find anything that we didn't know about because obviously we hope that the vaccines are safe and -- but it shows I think the importance here is not just to find problems when there are problems, the important is to show that the vaccine is safe when it is safe.

Just an example of something that was not found, these were not statistically significant, but these were things that we were actually looking for. Pure hypercholesterolemia, for example, or dysphagia, those are things that we could have found if there was a problem, but there wasn't a problem. So nothing of this was found. In the statistical (inaudible) we found two known adverse reactions and no candidates for further explorations and nothing that was we thought was due to confounding.

Now, we had 1.9 million doses there, so we had a lot of power, but you can do it with a few number of doses also. For example, MMRV vaccine. We did a test run on that, not protocol based, but a test run with 100,000 doses and we see here that the seizures, which was a known adverse reaction to this vaccine, shows up, as well as skin problems. So you can do this also with smaller samples as well, about 100,000 or so.

So some general issues to finish up. This worked well for HPV and MMRV vaccines. We found known adverse reactions, no false positive, adjusting for multiple testing. For HPV we have high power to take adverse reactions. One limitation is that we only looked for early onset adverse events. You could do it for late onset as well, but we haven't done that yet. So it's important to note that this is an exploratory tool with thousands of outcomes. We cannot do a careful adjustment for all potential confounders. So if there is a potential problem we have to follow-up with -- to confirm or dismiss these signals using more traditional (inaudible) methods.

There are other study designs one can use in addition to the self control tree temporal scan statistics depending on what the data looks like, like mass cohort designs or observed and expected counts, for example. And one should always be considering time varying confounders when using the self control methods, for example, concomitant vaccines, seasonal exposures, age, or other things. And Judy is also doing the reverse. Instead of scanning the outcomes we scan the -- we choose one outcome and scan the drug tree to see if there are adverse reactions. And there's a free software, the TreeScan software that can be used do these analyses.

So thank you very much. (Applause)

DR. FORSHEE: Thank you very much, Martin. Our next speaker this morning is Judy Maro. She is the Assistant Professor in the Department of Population Medicine at the Harvard Medical School and the Harvard Pilgrim Institute. And she's going to be talking about the patient profile components of the TreeScan.

TreeScan Patient Profile Component

DR. MARO: Hi, everyone, good morning. I'm going to be making a lot of allusions to things that our earlier speakers have talked about, hopefully to put that picture together so

you can see how this all comes together into one sort of pharmacovigilance or safety monitoring system.

So the first thing -- I think it skipped over -- I had a conflict slide. I have no conflicts. And so the first thing I wanted to cover here is that TreeScan essentially provides a mechanism that is complementary to the other pieces of the pharmacovigilance system that are already established. It does that by, as Martin alluded to, generating safety data on more than 6000 outcomes. So we're getting really complete coverage of things that we never previously had coverage of. One of the pieces of this is that we are complementary to something like FAERS where you're getting coverage of all outcomes, but there you require that there's some sort of a suspicion, as Craig alluded to in some of his earlier work today, that there's a suspicion that the outcome and the exposure are related, which causes a stimulation of a report and then gets in the system.

Additionally, there are specific studies that have been talked about. So this is what was referred to earlier today, the Vaccine Safety Data Link, has a rapid cycle analysis, Sentinel has the equivalent sequential surveillance activities. Those look at very particular outcomes and very particular exposures. And it usually covers something 5 to 10 outcomes. Because they're particular they're much more -- the confounding control and things like that are much more tailored to those particular outcomes, whereas we're looking for a much broader coverage.

So what is a TreeScan alert? One of the things that Martin had talked about when he showed his alerts there and he was referencing the HPV4 study with the cellulitis and rash, and then also with that sort of grab bag of other reactions related to vaccination, what we call those is we make a distinguishment, those are statistical alerts. So those meet a certain criteria to rise to that level, but they're different than signals. So what a signal implies is a regulatory sort of meaning. And what we want to make sure that we understand is we call something an alert and then we triage it. As Martin had alluded to before, we want to find things that are known adverse reactions. Those things aren't new safety information and so they don't constitute something like a signal, but they are an alert, meaning that we did find them in our system. As he said also, one of the things that is important to note is with these alerts there's a triage process and then we have to figure out whether there's a need for follow up or not. And as we went through this procedure with HPV4 we got to the end and decided, you know, there was nothing further to follow up because all of the alerts were known adverse reactions. And so it's an alert situation that then precedes the idea of calling it a signal. So I just want to make that clear, the distinction between alert and signal.

So one of the things we just talked about with the alerts being triaged, we start out with looking for things that are obvious known adverse reactions, so we can just reference the label. So one of the very common ones, the one that we found in HPV4, was the cellulitis and rash. We also can rule out possible adverse reactions that are due to time bearing confounding. So one of the examples that Martin sometimes talks about, but we didn't

talk about today, was work that was done on pneumococcal polysaccharide vaccine, where we saw an alert for spleen surgery. And this was a little puzzling to us as non clinicians, but for the clinicians in the room, when they say this, they said oh, of course, because people get this vaccine as a prophylaxis prior to their surgery. And so it's not that the vaccine causes surgery, but there is a temporal relationship there and we did detect it, which gave us confidence that the method is doing what it's supposed to be doing, but it is not in fact new safety information, it does not require further follow up. It's something that we can say we believe is attributable to time bearing confounding, which is that just prior to people getting spleen surgery they go and get this prophylaxis.

And so then we used this to narrow to a list of possible adverse reactions that might merit further follow up. And so we considered using what we referred to today as the Patient Episode Profile Retrieval Tool. So this is a little schematic of sort of the flow of information and how that gets to us at the Sentinel Operations Center. So at the Data Partners, we go out and we use our extraction program to get these data, we bring it back to the Sentinel Operations Center, we run TreeScan on it -- that was the software that you saw Martin reference with the link which is available for anybody free to download. When we get that we get those alerts and those are the things that popped up in that list that Martin showed where you see, you know, cellulitis and rash rise to a statistically significant level, which we would call an alert. We then go through that alert investigation. That's that initial triage process, where we say okay, is this something that's in the label or not. If it is it's an explained alert, it's a known adverse reaction. If it's not, it's not, it's an unexplained alert. And if it's an unexplained alert, we think about well can the patient episode profile retrieval tool help us to actually explain what's going on. And so an example of that that Martin already foreshadowed was that one of those codes in the HPV4 study was this kind of, I would call it a grab bag code of just adverse reaction to vaccination. And there was a list of things that were in there. And so the question was, is that an independent alert or is it really correlated with the rash, which is what we ended up finding. What can we do to understand this better? And so the Patient Episode Profile Retrieval Tool gets that data and brings it back to us and then we look at it in using what we call TEVR, which is this TreeScan Vaccine Episode Report, which basically is a way of saying it's a nicer way to look at this information.

So PEPR is a form of an alert investigation. We use it to retrieve de-identified patient level data. And so it's really important to understand that we're asking our data partners to return patient level data sets to us, but we only do it because we believe it's absolutely minimally necessary to continue to follow this alert. And so we do ask that they de-identify it. And what are the things that we might do to de-identify? We relativize all dates, we make sure that if we ask for age we break those into age strata or groups. We don't ask for very specific information that could lead to identification of a patient, we do as much as we can to sort of create disparatized groups of things. And we do that because we want to protect patient privacy, but also we want to use this as an interim step to decide

whether there's really a true signal there. As folks in the room talked about earlier today, one way to do this is just to go straight to chart review. Chart review is extraordinarily expensive in some cases, and it might be, for example, in this particular alert that we saw with the unspecified reactions to the vaccination, that it turns out that all of those codes really were indicative of cellulitis or rash, they were double coded for these patients in a different way. You know, finding that out via chart review is kind of a very expensive proposition, whereas finding out via the Patient Episode Profile Retrieval Tool allows us to narrow down our list of potential things that we might want to actually use charts for by looking at whether there is some sort of correlation or alternative explanation there.

So we think of our PEPR took with our TreeScan Vaccine Episode Report as some form of a poor man's chart review, meaning that we do our best to narrow down to really things that we think might be of interest and then potentially further follow up, if we don't rule out that point as saying oh, in this case, the one that Martin referenced with HPV4, it's a known adverse reaction.

So this is an example of an excerpt just to give you a sense. I'd like you to take a look at the top part of your screen right now. This is an excerpt that we used when we ran -- when we were building this system. And as Martin alluded to, we ran it with MMR and MMRV and we did this to test the system with something that we knew a lot about. One of the alerts that came up was nausea and vomiting. The nausea and vomiting alert was something that, as you can tell, is very non specific. And so we used it as a test case to see, okay, well if we go and pull this will we find more information that might, you know, allow us to see whether there's something independent or if there's a correlation or something going on. If you look up in that episode, you'll notice, as I said before, we don't bring back the exact age, so you see that this is a child who got this vaccine and they have an age band given to them. We don't bring back the exact date of their exposure. You can date of their exposure. You can see that it's the month of the exposure there. All the dates there are relativized, so we don't have any calendar piece of information, we can't track this back to any year of exposure. So it's only to give us the information that we need to sort of assess what's going on. And if you look at the episode detail, what we're looking for here is that we have evidence that this child was vaccinated, in this case for MMRV and PCV7 on the same day, and then they had this alert that came up for nausea and vomiting. If you look back in this patient's record in terms of their patient profile, they end up at the same time that they're getting their vomiting alert having a basically GI bug. So you have a very small child, you know, approximately one year old, who ends up in a one day in patient hospitalization for a GI bug, and that happens to occur seven days after their vaccination. We don't think it's actually a result of their vaccination, but temporally that's what happened and that's what we see here. And so what this allows us to do is then say, you know, we don't think this is actually vaccine related; we're going to rule this out. We don't need to go get an expensive chart in order to verify this. We can take a look and see what happens here and use the PEPR tool in order to sort of more efficiently go through our alert

triage process.
And so in summary, we use PEPR and its associated Vaccine Episode Report, to rule out a refine and alert investigation before proceeding to this more expensive chart review process. We only ask for minimally necessary information to come back, although it is patient level. Folks in the room can think of this as an analogous sort of source to a MedWatch case report where a case report is based on one patient and has a series of information about that patient. This is very similar in that sense.
And with that, this is a list of all the TreeScan team members and I would particularly like to highlight actually David Cole, who is not here with us today, but how did most of the work on building the infrastructure for this particular -- for PEPR and for the TEVR associated. And with that, that's all the slides I have for you.
Thank you. (Applause)

DR. FORSHEE: Thank you, Judy. If Judy and Martin could both join at the table we're going to do 10 minutes of question and answer, both from the audience and from anyone on line and then we'll welcome the rest of the panel members. So we'll go ahead and open it up now for any questions from -- we'll do the audience in the room first. And, Chris, do we have any questions on line yet?

MR. NGUYEN: No questions.

DR. FORSHEE: Okay. I'll kick things off then with something that came to my mind during the discussions. There was some talk about doing some power calculations for using the TreeScan tool, and I know that there is a larger project underway to consider that, and that ties in a little bit to the time it takes to accumulate enough cases after a new product comes to market in order to have enough power to really be able to look at this. And I was wondering if either of you would care to comment on what your early experiences have been about how long we really need to wait -- and I know it's going to vary by product, so I know there can't be a general answer -- but if you have any reflections on how long it seems like we're going to need to wait before we'll have sufficient power to run these sorts of TreeScans.

DR. KULLDORFF: So that's a very important question. And one thing that differentiated TreeScan data-mining methods from the traditional studies, in the tradition study you have one exploration, one outcome, and for that for a certain sample size you have a specific power. For the TreeScan, since you're looking at multiple outcomes, you know, in our analysis you're going to have very good power for one outcome and less good power for another. And there's no way around that. So that's sort of just a basic feature of the method.
So then the question is -- so in the example that we had here for HPV4 with 1.9 million, we

had very good power to detect some very rare adverse reactions that we actually could see from the examples. For MMRV we had very good power to find something like seizure, which is 1 in 2000, but ITP is another known adverse reaction to both MMR and MMRV vaccines and we did see that one with 1 million MMR doses, but we didn't pick it up with 100,000 MMRV doses.
So in a way, if you do this with a new vaccine, if you do it a little bit earlier, you can pick up the serious large adverse reactions that are like (inaudible) like seizure after MMRV, like 1 in 2000. But if you then want to pick up things that are 1 in 100,000 attributable risk, then you would have to wait until you have at least a million doses.
And maybe Judy wants to add to that.

DR. MARO: No.

DR. FORSHEE: Yes, please.

DR. HAYNES: This is Kevin Haynes from HealthCore. So I'll add a provocative statement with regard to TreeScan. And I really like some of the presentations. I think this might be the third or fourth time I've seen it. So vaccines have caused my kids to walk, you know, because you get them at well visits and then a couple of weeks later they magically learn to walk. So for those in the audience that work for manufacturers this might be something that you could -- but, no, to that point though, since vaccines are given at well child visits, and often things are picked up at a well child visit that then might require follow up within a few weeks -- so like my son has pectus and then we had to have cardiology to rule out a murmur. So can you speak to a little bit of these types of things knowing how healthcare is provided and how that then can induce some of these types of things?

DR. KULLDORFF: That's a very good point. And for HPV4 we didn't find any of those things, but we have for other vaccines. For example, one thing that has sometimes shown up is eye problems and that we think is because they come to the well care visit, they have an eye exam, they are told to go to the eye specialist, and then four days later or whatever, they diagnose some eye problems. So those do things do occur for some vaccines and some age groups in this. So it's sort of one example of time varying confounder that has to be taken into account if one evaluates any alerts coming out of the system. Similar to the spleen surgery, it's another example of a time varying confoudner.
Another time varying confounder is concomitant vaccines. We did this for the PCV7 vaccines and for the 12 month old there is an increased risk of seizures 7 to 10 days after PCV7 vaccine, but not at the 2, 4, and 6 month olds taking the vaccine, and obviously it's not due to the PCV7 it's due to the MMR or MMRV vaccines that they get at the same time at the 12 month visit.

So there are several of those time varying confounders that can generate false alerts. One has to always be very vigilant about picking those things up. So your comment is excellent, so thank you.

DR. FORSHEE: Judy, do you have anything to add to that?

DR. MARO: No, I just say that concomitant vaccines because it occurs so often we have built into the tree extraction program the ability to automatically bring back same day concomitant vaccinations. So we'll always have information about that right at the outset, whereas some of the other things, like the eye problems and things like that, you might actually get the alert and then follow up on it. So it's basically before or after kind of how to prevent these things.

DR. FORSHEE: And the only thing that I would add to this discussion is that in part for this kind of phenomenon we always build multi disciplinary teams for all of the projects that we're looking at so that just because we see something from a statistical perspective, we make sure we have medical officers and other people with more clinical knowledge involved as well so that we increase the likelihood that we'll be able to pick up on something that is just a result of the way healthcare is delivered in this country.
I believe I saw another question. And please give your name and affiliation, and thanks very much for giving your name and affiliation earlier.

DR. VELICER: Hi, I'm Christine Velicer with Merck Research Labs in the Department Pharmacoepidemiology. And I am wondering how you are dealing with the transition to ICD-10 within the TreeScan system knowing the very different number of codes between ICD-9 and ICD- 10?

DR. MARO: That's a great question. So as somebody from Merck you probably are aware that we have a protocol available and on line for Gardasil 9 monitoring that we are planning to do. And that includes obviously codes in the ICD-10 era. So we needed to come up with a way to ensure we are not only capturing ICD-9 but also ICD-10 codes, particularly because the release of HPV9 bridged the ICD-9 and 10 period. So we had to be able to accommodate both.
And so the ICD-9 tree that we use is put out by AHRQ, the Agency for Healthcare Research and Quality, and that's their clinical classification system. They also have one that they've published for ICD-10. Unfortunately, it's only two levels of a tree. So it's a really not very granular sort of way to look at things because it's very complicated. As you mentioned there's the immense sort of growth in the number of codes. And so what we've done is we've used what's called the GEMS, or the General Equivalency Mapping System, which is another AHRQ product, which basically maps 9 to 10 equivalent codes.

So it tells you, this is a 9 code, this is its equivalent in 10. It does forward mapping, it does backward mapping. And what we've done is we've actually mapped all the ICD-10 codes onto their ICD-9 code equivalent and then we used that in the overall tree, because we believe that the ICD-10 tree doesn't provide us the level of granularity we need. It doesn't take advantage of those different levels of aggregation that the ICD-9 tree has. And so we've actually had to incorporate sort of 10 into the 9 tree in order to keep all of those levels. And that's how we've chosen to address that problem.
Thanks for the question.

Panel Discussion:

DR. FORSHEE: I think we have time for one more question, either from the audience or from on line. Do we have another question before we move to the panel discussion? And, Chris, nothing on line?
Okay, great. Then I will go ahead and invite our panel members to the table. We have Eric Weintraub, Frank Rockhold, and Walter Straus. And I'll give more introduction once everyone is settled.
Welcome, everyone, and thanks for coming today. So our panel members are Eric Weintraub, who is an epidemiologist at the Centers for Disease Control and Prevention, we have Frank Rockhold, who's a Professor of Biostatistics and Bioinformatics in the Department of Biostatistics and Bioinformatics at Duke University, and we have Walter Strauss, who is the Associate Vice President in Therapeutic Area, Head Clinical Safety and Risk Management at Merck Research Laboratory.
Each of the panelists is going to have five minutes to talk about some of their impressions of the session so far and then we'll open it up again to questions from the audience and on line.
And I'd like to start with Eric providing the first five minute commentary.

MR. WEINTRAUB: Thank you. Again, I'm Eric Weintraub. I'm a Project Leader with the Vaccine Safety Data Link. I've been involved in vaccine safety post licensure studies now for approximately 15 years, and the VSD has a long-standing history in rigorous vaccine safety studies, traditional studies, rapid cycle analysis, real-time surveillance. As new vaccines enter the market and as changes to those recommendations occur we typically implement a study. So in the '90s and in the early 2000s the VSD explored data-mining methods and conducted mostly screening studies, similar today to mining, where you would screen for a laundry list of adverse events following a specific vaccine and then treat these as hypothesis generating and follow up on specific things that were elevated depending upon the design.
We've somewhat historically -- Martin has been involved at the VSD as long as I have I think. We've always been cautious about data-mining in VSD for various reasons, the cost of following up false signals, many chart reviews, the burden of these chart reviews,

there's a high -- as mentioned before, particularly in the vaccine safety studies -- there's a very high gold standard to conduct chart reviews for many outcomes. And particularly in the VSD, as the EMRs get -- you know, we've had EMRs since 2006, it's very easy for us to conduct chart reviews at this time, but it's still an expensive process.

And then one of the other key components that Frank reminded me of was there was a big school of thought in the early 2000s about finding a signal in a population and then also testing it in the same population. So we've had discussion of do you hold back a large site to then do a confirmatory study. And now, you know, we have VSD, we have PRISM, you have essentially some complementary systems. So I think there's been some discussions on how we can work together in this capacity for one system does hypotheses, generating signal detection and using TreeScan data-mining, and then maybe the VSD does the confirmation, et cetera.

As mentioned earlier, the VSD, you know, pioneer rapid cycle analysis does real- time surveillance as vaccines enter the market. And as mentioned, this is on a limited number of outcomes. We would look at what was from a pre-licensure trial, similar vaccine profiles, and then, you know, look in real-time at five to ten outcomes, obviously, not the entire ICD-9 code book. So we always felt that we needed something to complement rapid cycle analysis, so we would complete a rapid cycle analysis and say, oh, everything's fine, we didn't find any elevations or protective effects of these five to ten outcomes. Meanwhile, there's a laundry list of ICD-9, ICD-10 codes that were not evaluated. So we felt we needed something to complement that so that we had a complete picture of the safety profile of the vaccine.

So for the VSD, as I mentioned, TreeScan -- you use the term very well -- is complementary to existing tools. We have traditional EPI studies, we have rapid cycle analysis, we have lots of varying methods now, self controlled case series, case control studies, case centered analyses, Martin's temporal scan statistic, which is a very valuable tool, and then now you also have TreeScan. So it's an important tool for the entirety. When you can use all these different methods it's a great tool to evaluate the safety of a product.

So, lastly, we've actually used TreeScan. We've implemented it looking at -- we have a study protocol. Back in 2006-2007 we looked at real-time at the safety profile of Menactra, and particularly there were some concerns over a GBS. We never conducted a conclusive one time study looking retrospectively at Menactra. All the focus was always on GBS. So we have a protocol in place to look at the safety profile of Menactra and the VSD, and we felt it was the perfect time to then also implement a TreeScan study looking at meningococcal vaccines, but for the most part in VSD Menactra was the primary vaccine utilized. So we have implemented a vaccine safety study using TreeScan, looking at Menactra vaccine in the VSD. I won't tell you everything. We consider this a test, a pilot. We have done similar things where we've done profile reviews, haven't necessarily gone to chart review yet, and as one of the questions was brought up, what we found,

particularly what you'll see with a lot of adolescent vaccines in particular, is like HPV does one as their seasonal. They come in in August to get -- they're coming in for sports exams, physicals, et cetera, so it's a screening. Kids come in and then all these other things are screened. So we found a laundry list of things that probably would be screened at a well child visit/well care visit, eye disorders, there some respiratory things, but lots of things that seemed screened. So what we did as well is we also ran -- we replaced the vaccine with preventive care visit, so we looked at people in the same age group that had preventive care visits without the vaccine and essentially found the exact same thing. So we whittled our list down from, I think it was 40 outcomes down to about 15. And even of the 15 very few were concerning.

So it was a very promising tool to add to our arsenal and I'm sure we're going to continue to do more work. And we actually have a protocol that we've pushed forward that should be finalized soon where we can implement it for any vaccine at any given time and all we have to honestly do is just change the exposure of interest and run a program.

DR. FORSHEE: Thank you very much, Eric. Frank, you have five minutes for your observations.

DR. ROCKHOLD: Thank you. Appreciate the opportunity to attend and comment. I'm going to comment from two perspectives. One is that they're related. I'm a statistician involved in designing and evaluating pragmatic clinical trials, both as an advisor to PCORI and at Duke Clinical Research Institute, using PCORnet, which is a similar analogous system to Sentinel using electronic health records, based on a lot of the same technology that Sentinel has developed, and pursing the use of these trials and evaluating safety. And so a lot of my questions are sort of questions and comments relative to that experience.

There is actually quite an interesting pragmatic trial going on right now in vaccines, trying to look at the use of flu vaccines to prevent myocardial infarction. So that will prove an interesting experiment.

DR. FORSHEE: I'm sorry, could you speak a little closer to the microphone?

DR. ROCKHOLD: Oh, I'm sorry; sure. Do you want me to repeat any of that?

DR. FORSHEE: Just continue.

DR. ROCKHOLD: Okay. Clearly there is a lot of value to PRISM. I mean having a denominator is a huge advance over looking at spontaneous events. One of the things -- I'm going to lump my comments into things I think -- additional benefits one could think about, and some of these were mentioned earlier today. I actually think that there is

a reason to believe -- and somebody mentioned this earlier about looking at effectiveness or benefits in the same system at the same time, and I know that's been discussed through some of the earlier OMOP work that was then transferred into Sentinel. So I think that's something that we ought to go back and think about. It's the same codes and I think TreeScan in particular should allow you to refine those.

And I'd like to extend the comment that was made by the gentleman from Vanderbilt. He was talking about using previous observational studies or epidemiology studies. I didn't hear much discussion about how the information from clinical trial is used to create prior information to look for these signals. I mean there's a lot of signals that either demonstrate it or suggest it in clinical trials, and it seems to me you could refine the estimation and use that actually as either a prior model or just prior information. And I think that would actually help you map some of the granularity from TreeScan.

Some of the issues that I would see -- and I think some of these have been -- I think Judy alluded to some of these -- one of the things we find in doing pragmatic trials in looking at, let's say, preventing myocardial infarction, the error rate in what gets coded in electronic health record is substantial. So if you're doing a randomized trial you can put up with some of that noise and just say well that's the noise of the experiment and I can still get an unbiased estimate of the signal, but the actual rates themselves are not going to be correct. And in discussions we've had with the other part of FDA in looking at doing safety studies for safer diabetes products and looking at pragmatic trials, one of the concerns they have -- they're not actually concerned about the scientific question, about whether or not you can evaluate or discharge a signal, but the question is then what rate do you put in the label, because the rates that you're finding in electronic health records, unless you go back, as Judy said, and do a chart review. So we're trying to investigate some mechanisms to do algorithmic chart review, maybe not different than what was described, to try to compensate for that.

One thing from Martin's talk that I -- several things -- I thought it was a very good talk and I think the TreeScan technology has some potential benefits, and I was really glad to see he was approaching some of this using absolute risk. I think one of the problems in the safety area is people using relative risks and people then not understanding. One caution I would give or plea is really be careful about using p-values. I think that the -- I understand how you're using them, you're using them to distinguish between a signal and trying to look at a particular effect. And I thought your description of that was excellent. Signal is one of the least well understood words in the English language. If I were to as 14 people what the definition was signal was I'd get 32 definitions. So I think it is really important to do that. But if you follow the literature recently, there's obviously -- as a result of a number of journals actually banning p-values from their publications -- I would encourage everyone to read an educational document put out by the American Statistical Association trying to explain to the public p-values. I'm sure you understand them. My concern is people will look at the p-value and not pay attention to the estimate. It's the estimate that matters, not

the p-value. So getting an estimate in a confidence interval is far more important. People will walk away with a very impressive p-value with lots of zeros, but not necessarily understand the public health impact. So that's just a plea.
The heterogeneity question I asked Jeff earlier, I think in the TreeScan, the heterogeneity is only going to increase as you go down the tree between partners. So I guess I would have a question to the FDA, how do you deal with that? (A) you have a coding problem, so you have events in a health system that aren't necessarily accurate, exactly what happened, and then you have tremendous heterogeneity on how that happens between partners. So how do you accommodate for that in a label when you're actually trying to describe a rate?
And the last part, I guess it would be interesting -- it was alluded to in the talk -- how does this actually fit in the -- TreeScan or PRISM fit in the sort of the triage system of the other or 18 other methods that are available for signal detection? It was alluded to a little bit, but I think having some better understanding of the governance process about, you know, is there some sort of strategy about when this is invoked.

DR. FORSHEE: Thank you very much. And, Walter, five minutes for your comments.

DR. STRAUS: Thanks very much. Good morning, everyone. So I am not a statistician, I'm an epidemiologist who recalls having been -- heard from this. One of the founders of the CDC who once said that there is not epidemiologic problem that couldn't be solved with a pencil, a piece of graph paper, and a ruler, and a 2 by 2 table. So how far we've come. So I have these sort of industries seated at this panel, so I'd like to just begin by stating the obvious, that there's a particular societal need for having a system in place that efficiently and effectively monitors the safety of vaccines following licensure. That sort of system assures that the benefit risk of recommended vaccines is well understood and it provides insurance in the integrity of the public health system.
Now, for some years the U.S. has had what is one of the most, if not the most, comprehensive post licensure vaccine safety assessment set of programs in the world. But we all realize that there's room for improvement. The VAERS spontaneous reporting system, which his kind of the bedrock of the whole thing, serves a critical role, particularly in the relatively prompt identification of rare adverse events, but it has well known limitations. The vaccine safety data link is able to formally evaluate potential safety signals through traditional epidemiologic methods as well as more recent developments, such as rapid cycle analysis. But it draws on a smaller patient population, maybe somewhat time consuming. And working in the private sector it's worth noting that vaccine companies themselves continually collect safety data following licensure and may conduct a range of additional safety investigations as appropriate.
PRISM investigators have focused their primary attention on what's been called signal refinement, which fills the gaps between VAERS and VSD. And TreeScan is one of the tools that's been developed in this context. As Martin has explained during his

presentation, TreeScan is a very clever approach designed in part to identify what have been called unknown unknowns. That is, novel exposure event combinations that may merit additional review. Working with large data sets that were derived for administrative and billing purposes, TreeScan conducts statistical tests on a very large number of exposure event pairs over a number of time varying exposure windows. And the output prevents findings that are not really potential signals. And I fully agree with the points made around the ambiguity of the term signals. They're not really potential signals in the manner of spontaneous reports, but might be rather considered to be topics for further consideration.

The two validation studies that were presented here for HPV and for measles, mumps, rubella, varicella vaccines, successfully identified know adverse reactions, that is known knowns. For HPV4, several other exposure event pairs were identified, they were subsequently disqualified due to confounding.

And apart from the limitations that have been previously acknowledged, on open question that I pose is the timeliness of TreeScan findings. What are expectations for the identification of TreeScan topics or alerts in comparison to currently existing methods, be it through VAERS, the sponsor, or others?

As TreeScan is deployed I'd like to pose two questions for consideration. The software, as mentioned, is currently available for free download. Validation testing has been done with external and established research partners, which suggests some measure of quality control. What are the intent and the expectations of providing the software for broad public use? If the software is not useful without a large, very large, database, who are the potential additional users? If a small database can effectively be used what might investigators hope to find that would not already have been find by larger database users? And since the data sources derive from -- rely upon administrative data collected not from research, but for reimbursement purposes, what are the thoughts about international use of TreeScan in countries in which healthcare economics may result in different use of diagnostic and procedure codes or approaches to using those codes than in the U.S.?

And, finally, one outstanding area is in communication. Prior to finalization, Sentinel protocols have been made available for public comment. This is very helpful as it provides an opportunity for those interested, including industry based researchers, to provide technical suggestions. If TreeScan is deployed more broadly in the future, what are plans for additional engagement as Sentinel investigators undertake and review analyses on new products? As the Agency tries to balance transparency with avoiding raising concern about numerous false positives that will be resolved with additional review, what's the appropriate level of and timeliness for public awareness? Sponsors will certainly be interested to know what issues are coming to the attention of the Agency through TreeScan so that they may be able to properly and promptly address these safety topics or safety alerts that have been identified through TreeScan, and more broadly through PRISM. And these may range from additional internal research conducted by the

sponsor, to product labeling and external communication issues.
Thanks.

DR. FORSHEE: Thank you all very much. Before we open it up for questions from the audience I want to create a brief opportunity if Judy or Martin want to respond to any of the comments from the panelists.

DR. KULLDORFF: I thought those were excellent and very thoughtful comments by all three panelists. So two comments. One is I agree with Frank, that attributable risks are so much more informative than relative risks certainly in this setting. Now, when you do TreeScan, while the p-values are unbiased and correct in terms of the (inaudible) processes and keeping the right alpha level, the table for risk has to be taken with more care. One example is the cellulitis example where the risk was 1.3 per 100,000. Now that's not an accurate risk for that for two reasons. One is that most people who get the rash they don't go to the doctor because it's very mild, and also they're just classified in different ways. So if you really want to know what is attributable risk of rash we shouldn't use that number. We'll have to do some more proper pharmacoepidemiologic study.
The opposite is also true. There might situations where they code something and only maybe the positive predictive value is only 70 percent. That will also create a biased attributable risk. So one would have to then sort of take the next step to actually calculate what is an attributable risk. So when using TreeScan one should always sort of take those attributable risks with caution and look into it further for those (inaudible).
In terms of the TreeScan software, we actually have sort of two software here, when doing the system. We have a tree extraction software, which was originally in science. That stands specifically for the Sentinel system, and that I think is not very useful outside of Sentinel because you have to have it in the Sentinel data model to be able to use it. And then there's the TreeScan software which is just like the statistical calculations. And it's the second part that's free for anybody to use. And I guess the potential users are for vaccine or drug safety surveillance would be other groups who do these things. VSD is obviously one, but there's also in Europe and other countries that they have systems, so they could also use it for their data. It could also be used by -- for completely different things, like occupational help, which is unrelated to drugs or vaccines. So it's like a general statistical matter than can be used in many different settings, not just for pharmacoepidemiology.
And then it can be -- I know one of the pharmaceutical companies is using it for product quality control where the tree is not (inaudible), but the tree is sort of different batches of the product and then they see what -- if there's some manufacturing plant or some particular batch that has a problem, so that's another type of thing that one could use it for.
So that's the reason we sort of made it free so that people can use it in very different settings and not just for pharmacoepidemiology.

DR. ROCKHOLD: Thank you for that, Martin. I totally agree that the attributable risk can suffer from underreporting and therefore the actual -- less underreporting than spontaneous reporting, but still potentially -- so I'm not opposed to presenting both the relative risk and the attributable risk. I think those are two different measures. What I worry about is that people -- that's why I made the comment about the p-value. It's easy for people to walk away and not actually pay attention to the public health impact there. I'm sure you're not doing that, but I'm -- it's more the other people who get access to the information, the public. You know, so that's what I worry about. So having some context around well if it's a relative risk, so that tells me there's a potential signal here, however you choose to define that, and the impact of the signal is measured by this attributable risk. So it's sort of my mission to get people to focus on the estimate and not the p-value.

DR. KULLDORFF: I agree with that. And the example for the cellulitis, that it was 1.3 per million, and the p-value was.00001, that p-value sounds very scary maybe, but 1.3 per million for rash is not scary at all. So I completely agree with that. And I also like that you made reference to the ASA, American Statistical Association, document because I think that was very excellent they stated. I thought that was a very good document to sort of dispel a lot of myth and misconceptions about p-values.

DR. FORSHEE: Okay. I'd like to open it up to the audience. Judy, did you have anymore? Okay. Then let's go ahead and open it up to the audience for any questions that they have for the panel.
Please. And just remember to state your name and affiliation.

DR. GUTSCH: Sure. Hi, this is Dave Gutsch with Regulatory Affairs for Merck Research Labs. I think Frank it was that brought up a really good point around accounting for the randomized control trials in the pre-licensure era. And I see that you have some success with these signal detection methods of picking up known events, but it seems to me like you should really be able to -- that being sort of a gold standard, you should really be able to detect every event that is, you know, at least powered enough where you would expect to see, you know, a difference. And you should also expect that these systems would then, you know, prove that ones that in those trials where there's sufficient cases has no difference, also have no difference in your system. And if not, you know, explaining it in the case that it might be real world situation, a different -- you should be able to come up with some kind of a plausible mechanism for why you don't see those.
So the question is how comprehensive is your validation of the pre-licensure database, you know, that supposedly gold standard.

DR. KULLDORFF: So the only way to really know the answer to your question is to do this many, many times with different vaccines and see how it comes out. So we only have limited data now from a few pilot studies. So I think for HPV4 there are no other known adverse reactions than the ones that we found with one exception, and that's syncope. It's a known adverse reaction to HPF4 and we did not pick that up. And the reason is that syncope normally happens within an hour after vaccination and we did not include day zero in our evaluations, so we included -- looked for things that happen from day one and on. So that's why we didn't pick up syncope. I guess if somebody got a vaccine at 11:30, just before midnight, we could potentially have picked it up just after, but I don't think that's a common time to get the vaccine, so I think for HPV4 it was very comprehensive in terms of things that happen one to six weeks after vaccination. We did not look at day zero and we did not look beyond six weeks. But within those six weeks I think we found the known adverse reactions and there are no other known adverse reactions.
And we had very good power with 1.9 million doses to actually have power to detect even very rare things. So I think we feel fairly confident there that it was very broad and we can sort of say that the vaccine is safe in terms of early onset adverse events.
For the MMRV, where we had 100,000 doses, we did pick up the seizures, which happens in 1 to 2000 people, but we did not pick up, for example, ITP. That's much more rare and I think that was a sample size issue. When we looked at the MMR vaccine with one million doses we did pick up the ITP also. So if we have 100,000 I don't think we can say we have comprehensive complete determinations of all potential adverse reactions, but we are able to pick up things that are more common that happens in 1 in 1000 or 1 in 10,000, or that range, but not things that are more rare than that necessarily.

MR. WEINTRAUB: Can I add to that too, Martin? From the perspective that it's a completely different study design as well, where you're comparing to time essentially versus other vaccines, placebos, et cetera. So sometimes you could except to get different things or not see certain things. I mean, some outcomes are going to be extremely exposure driven, so you know they're going to be elevated in a certain time period compared to other time. Syncope is an example where it occurs day zero, one, and doesn't occur the rest of the time, anaphylaxis and other things. Some outcomes just aren't going to be perfectly suited for this type of time analyses where you're going to have to use another vaccine as a comparator, for example.

DR. MARO: I'd just also like to add that in general the data that we're using here to power these analyses are the claims data as has been alluded to. And so you really have to have medically attended events. So if people actually have reactions and then they don't actually seek medical attention we're not going to have those in our data, we're not going to see them.
We also have made a deliberate choice in these pilots that we may choose to expand upon

later, to only look for outcomes in the inpatient or the emergency department setting. That choice was made to look for serious events, and with the marker of serious as -- you know, Jeff Brown actually talked about it much earlier, the outpatient diagnoses are not audited, whereas the inpatient information is auditable. And so we feel that it's very confident that it's actually indicating that something is really important that's happening. And so choosing to look in the inpatient in the ED setting also will change whether or not it makes into the label.

So Eric and I were just talking here about headache, for example. And so a headache is primarily going to be an outpatient event, if it's medically attended at all. If it's medically attended and it's in the inpatient or the ED setting it's probably in addition to five or six other diagnoses that happened on that same day. And so there's going to be -- in terms of a comprehensive look at what are all of the things that were discovered in the clinical trial and can we find it, yes or no, every single one. It's going to have to be very deliberate in trying to see what you could find based on sort of the presentation of this in the clinical system that we have.

DR. STRAUS: I wonder if I could ask a question. So I'm thinking about syndrome identification, and syndromes in which they may be comprised of discreet diagnostic codes that would heretofore be considered to be unrelated. And the one that just comes to mind is something not from vaccines, but it was the world of nutraceuticals a long time, Eosinophilia- myalgia Syndrome. People would not normally put together Eosinophilia and Myalgia. And I'm wondering in your methods, it sounds to me as though you roll up, you know, within leaf to branch and bigger branch, but do you do any comparisons across branches to identify, you know, patterns that are seen between different branches to allow for syndrome identification?

DR. MARO: So when we do the analysis we're looking at -- so we're a little bit taking for granted that the tree has actually clustered these outcomes in clinically meaningful sort of ways. And then we don't look at say, you know, how much of the skin part of the tree has been lit up versus how much of the musculoskeletal system part of the tree. If you have particular interest in a particular type of syndrome you could create your own tree where you would aggregate a series of ICD-9 codes and say, you know, when this is seen together, this level of aggregation comprises this clinically meaningful definition. So we're at this point taking the tree as fixed from the Agency for Healthcare Research and Quality. We've also tried other trees. We've used the straight ICD-9 tree. So, for example, you know that itself is a hierarchy. And so we've used that and we've compared that to doing work with just the clinical classification system. But anybody who wants to go through the work to create the tree, you can do that and then actually look at those codes accordingly.

And so, things that branch across -- so and to say the clinical classification system itself is

body organ systems, so the way that it's oriented, so if you have something that reaches across that, you know, looking to develop a tree that actually does that would be a wonderful addition to sort of the work that we're doing.

DR. FORSHEE: Okay. I'm sorry, please go ahead. And then I'd like to go back to the audience for any other questions.

DR. ROCKHOLD: So just to bring back that clinical trial piece again, I guess I'm a trialist by nature. If I would then switch to -- I understand all your comments about some events are not going to be detectable in a trial, and I get that. You know, syncope would be a good example in terms of time. But if I were to now switch to looking at effectiveness, I had really good power in the trial to detect effectiveness, otherwise the vaccine wouldn't be in your system. So it seems to me it's a natural extension of that. One of the things you struggle with in the post marketing arena is it's all about benefit to risk, it's not just about the risk. But the benefit is assumed because it's assumed based on what I saw in the trials. And rarely do we get any new information. But it seems to me here's a unique example, the ability to say okay, I actually have the ability to detect okay, I've given this population the vaccine, is there -- and I don't know the answer, but I'm just -- can I take that -- the prior information from the trials, I know what the effectiveness rate should be -- let's just take flu vaccine -- can I then project forward and say is that what I'm actually seeing in the system. I mean you -- and it may be -- it's kind of like taking a pragmatic trial and sort of turning on its head and just saying okay, I've got a prior, can I actually look at the information on a daily basis saying but how does that -- what's the posterior probability of effectiveness?

DR. FORSHEE: Yes, so let me just say that we're actually going to be discussing some of those issues in Session 6 today, including talking about a post market observational study of the relative effectiveness of high dose versus standard dose vaccines. So, yes, Martin, and then we'll go back to the audience.

DR. KULLDORFF: Yes, so the TreeScan method doesn't really look at effectiveness of the vaccine. So that would have to be like a secondary -- for HPV4 of course we didn't find any problems with it, so obviously the benefit is better than the harms. But if we found something that was a serious thing, then that would be a problem for CDC and FDA to figure out what is the balance there. And I don't think TreeScan can do that directly. We'll have to use other methods. That's my gut feeling.

DR. ROCKHOLD: Yes, my apologies. I wasn't being specific to TreeScan. Sorry. It was a more general comment. Sorry.

DR. MARO: Can I just add one thing just to clarify, because this goes back to what Eric had said before. The TreeScan design we've been basically talking about self control

design, so it's really about the timing. So, you know, you're looking at one period of time and comparing it to another period of time. And I think something like that you would need a different design.

DR. ROCKHOLD: Yes, sorry. I was asking a more general question about the database itself. Sorry.

DR. FORSHEE: Yes. And again, I think we'll come back to that a little bit later. I would like to make sure we give some other opportunities if there are other questions from the audience.
Yes.

DR. IZURIETA: Yes, I'd like to go back to --

DR. FORSHEE: Hector, please, name and affiliation.

DR. IZURIETA: Sorry. Hector Izurieta, FDA. I'd like to go back to comments by Judy Maro and Walter Straus, and I will try to be brief.
We usually have the problem of we find the signal, we find an outcome, and then we need to do medical record review. That takes time, that is expensive, it's complicated, et cetera. But I will try to address this from another perspective and see whether you have other comments. When we do medical record review we really are trusting a reviewer, his time, his completeness, his reliability, and also the piece of paper we have and how complete this piece of paper is, how much information it has, et cetera.
So I'd like to propose that medical record review is not really as traditionally considered, the best way to confirm a diagnosis. If I have a disease I go to the doctor and I try to present the patient to the doctor and say that this patient has this disease. If we use this premise, then I would say the real purpose, at least one important purpose of a medical record review would be to verify, for instance, in a hospitalized case, whether is this a primary discharge diagnosis, is this correct, yes or no. So there is a primary discharge diagnosis. Second, was that discharge diagnosis provided by a specialist of the appropriate specialty. And that for me is the end of the medical record review. If I responded positively to these two questions and we can use claims to respond to these two questions, we can use primary discharge diagnosis, which almost by definition confirms it is a discharge diagnosis. And second, we can use in some systems, certainly Medicare, the origin of the claim as a specialist in rheumatology or a specialist in neurology, et cetera. I could elaborate if there is interest, but what I mean is at one point I'd like us to really discuss what medical record review is and how we can efficiently use it in claims.
DR. FORSHEE: Okay. And I see we only have a brief time to respond to that, but please.

DR. WEINTRAUB: I can real quick. Not from a PRISM perspective, but from VSD. We actually have a process that's very similar to that, we call it quick review process where we've tried to go away from a 40 page chart abstraction form and rely on the medical diagnosis and then was it diagnosed by a specialist.
What we found a lot of times is, you know, we do have high positive predictive value for a lot of codes. The problem typically is the onset of the illness in relation to the exposure. So a lot of times we feel very confident that, yes, this is diagnosed, it's GBS, and it was diagnosed by a neurologist. The problem is what was the onset of symptoms. That sometimes can be when you need to dive in a little more and where you might need additional information, and in particular if you're going to do some Brighton Classification. But we've done a lot of work where we need an answer quick, we ask four questions, confirm the date, was it confirmed, yes/no. Done.

DR. FORSHEE: Do we have time to take one more question? What's that?

DR. MBA-JONAS: Thirty seconds.

DR. FORSHEE: Okay, then that would be no we don't. (Laughter) I want to thank everyone very much for their participation in this session. I really appreciated the discussion among the panel members. I thought that was very enlightening.
I believe we're going to lunch next, so thank you all very much. Enjoy your lunch and we'll be back at 1:00 --
SPEAKER: (Inaudible).

DR. FORSHEE: I will turn it over to Joyce.

DR. OBIDI: So, briefly, for lunch I just wanted to let you know that there's actually two cafeterias. There's one downstairs, but then there's one about five minutes -- it's a five minute walk. It's at the Natcher Building and it's a larger cafe, it has more options. So you're more than welcome to go there. And if you have any questions you can always ask any of us up here. And we'll be back at 1:15.
Thank you. (Applause)
(Recess)

Session V: Stakeholder Feedback about PRISM

DR. ANDERSON: All right. To keep this on time, we're going to get started. This afternoon session, Session V, is the stakeholder feedback about PRISM.
I was just going to take a few minutes to introduce the panelists, and then make some comments. Who did I just lose?

DR. CHADA: Harry Seifert.

DR. ANDERSON: Harry is right there.

DR. SEIFERT: I tried to hide. (Laughter)

DR. ANDERSON: Harry! All right. Going down the line, I can't see all the name tags, so I might call you differently. I hope they're in order.
The first person is Christine Velicer, who is the Associate Director for Epidemiology, Department of Epidemiology at Merck Research Laboratory. Thank you for joining us.
Frank Destefano, who is Director for the Immunization Safety Office at the Centers for Disease Control and Prevention. Thank you.
Our late arrival is Harry Seifert. He's the Senior Director of Pharmacovigilance Alliance, GlaxoSmithKline. Thank you, Harry, for coming. James Stark is the Director of Epidemiology, Pfizer. Karen Bok, who is the Senior Vaccine Science Advisor at the National Vaccine Program Office, and then last but not least certainly is Bob Davis, the Director of the Center of Biomedical Informatics from the University of Tennessee.
These are the panelists. I was just going to make a few comments. This session really is about transparency and communication. The purpose of this is obviously for the panelists to give their opinions and their feedback about PRISM.
I was just going to take a few minutes to talk about the way we try to make PRISM transparent and the communication actions that we have taken. For protocol based assessments, as you're probably aware, which are the most comprehensive of the epidemiological studies we do in PRISM, we post the study protocols on the Sentinelsystem.org website. That's a fairly new website. I think it was launched within the last two months, I believe.
The process is that protocols are open for two weeks for a public comment period, comment period closes, and then FDA, our office, the Office of Vaccines, as well as the Harvard Pilgrim Sentinel researchers, review those comments. We consider them and make changes to the protocol as necessary.
Finally, obviously, we move forward with conducting the study and then generate a draft final report. We post all the reports on the website. I'm sure many of you have seen those. Prior to doing that, I think the critical thing is that we inform manufacturers and sponsors before posting the protocols or final report that involves their product.
One key point is I think we do it 24 to 48 hours before, so I think one question is is that sufficient. The next thing I wanted to talk about is REO analysis and more rapid query type assessments, the code for the analyses are usually posted on the website as well. Again, that's just another step in transparency where we are trying to just be as transparent as possible, communicate what we are doing as far as studies.
As far as FDA communications, major findings from the PRISM studies, as you saw in

some of the talks today, are posted. We can post anything from a safety communication to just a communication on the FDA website about the conclusion of the study and any of the findings.
As far as publishing the work, many of the findings of the protocol based assessments in studies are published in peer review journals. We have public meetings. I'm going to call our attention to this meeting. This is one of our opportunities that we take to again communicate about the program to the public, and hope for an interchange with the public and exchange of information, comments, and feedback.
We also have an annual Sentinel workshop that's hosted by the Duke Margolis Center. That is an FDA enterprise. We talk about the entire Sentinel program. This year's coming meeting will be on February 2, 2017 in the Washington, D.C. area.
Finally, CBER and Harvard Pilgrim staff present the PRISM studies at scientific and other types of public meetings.
Basically, what I'm trying to say is we have a lot of these various ways that we try to establish communications. We also are trying to move forward with taking some of these projects and doing informational presentations at our advisory committee meetings as well. For instance, the BRPAC meeting, just presenting the findings from a large study.
We are moving forward with trying to do that in the future as well, because we think it is important to get expert feedback in addition to sort of the peer review feedback we get on the journal articles. We are looking for outlets and ways to do that any way possible.
I'm going to stop there. I look forward to comments and feedback on the program. Christine, would you like to start?

DR. VELICER: First of all, thank you for the opportunity to be here. I think this is a really great forum to discuss vaccine safety.
I'm the lead epidemiologist for HPV vaccines at Merck, so I have a lot of experience with the two-week turnaround comment period. Two weeks is really small sometimes, really short.
My first experience was with the VTE protocol. I thought the protocol was very timely. We had seen in the literature the VAERS assessment that showed a disproportionate analysis, disproportionate reporting for VTE. Followed up by the VSD study, which had a non-significant finding but raised a question and sort of continued. We now had two things that raised this question.
Simultaneously at Merck, we had, I think, just finished our safety study that was in Kaiser in Northern and Southern California. We had not identified VTE as a potential alert. I was very interested to accrue more information so that we could miraculously assess whether there was a risk.
At issue, as was mentioned earlier, was this concept of confounding through oral conceptive use. I think the PRISM protocol to look at that was very timely. I appreciated the opportunity to be able to provide comments on the protocol.

If there are things we have learned through our safety study and observational study experiences, we are very happy to share that. These studies do take a lot of thinking and a lot of collaboration and discussion to make sure we are using the best methods available to us. We share the goal of having good understanding of safety.

I'm happy to say I feel like the comments we submitted were addressed, were heard, and reflected, and that was very nice to see. I thought the final report was clear. One thing I liked in the report and I think the FDA communication as well was it reported the findings in a larger context. It brought together the VAERS and the VSD study, provided the results of the Sentinel study, and during that time period, a few more observational studies had been published and also had no findings.

I think it really helped shore up the knowledge that had been accumulated to date, and I thought that was very helpful.

My second experience was with TreeScan. I had a lot of questions on the TreeScan protocol because it was very new and because Gardasil was a pilot test. I really wanted to make sure that we understood as best we can what the methods were.

Subsequent to that, the Gardasil-9 TreeScan protocol came out. I had very, very few comments. I think that was because many of the questions and concerns and confusion that we had provided in our original comments were actually addressed in the protocol, and that was really nice. Again, it felt like our questions and comments were being heard and thoughtfully addressed.

I believe I first found the results of the Gardasil pilot test in the introductory section of the Gardasil-9 protocol. I was happy to see the findings. It was an interesting way to find them. I think it would have been -- I don't think the report had come out, the pilot test report had not come out prior to the Gardasil-9 TreeScan protocol.

I think that was one area that if there was any way to have had results beforehand, that would have been helpful. Nonetheless, I was really surprised to see how amazingly consistent the findings of the pilot test were to our own safety study with Kaiser, the cellulitis. That was very reassuring.

DR. ANDERSON: Good.

DR. VELICER: One question I have or thought that I have is what if an alert were generated as a result of one of these, for example, a TreeScan analysis, and would we have sufficient time to be able to absorb, read, understand the findings, as well as CBER and Sentinel, would the manufacturer have enough time to be able to thoughtfully understand the issue?

We would have the need to globally disseminate a message, and that does take time and a lot of thought and care, because we want to make sure we understand the issue and we can adequately convey it. Thank you.

DR. ANDERSON: That's an important point. Thank you.

DR. VELICER: Thank you.

DR. ANDERSON: Frank?

DR. DESTEFANO: Thank you for inviting me to participate in this workshop, and FDA and others who have been involved in putting it together.
I've been working on the vaccine safety data link or VSD for several years, so I guess I would bring a perspective like sort of lessons learned in that project and see how they may apply to PRISM.
First of all, I'd like to laud your efforts in transparency, communication, and engagement. I think you are doing a lot of really good things there.

DR. ANDERSON: Thank you.

DR. DESTEFANO: One of the questions I want to address is our current PRISM capabilities. I give kudos to everyone involved for the capabilities that have been developed in a relatively short time in PRISM. It well demonstrates the capabilities for what you call your "protocol based analysis" and completed studies there. I also would highlight the HPV4, and the venous thromboembolism study in particular.
I think the work you have done in methods development is a real strength, and I think TreeScan holds a lot of promise, and as you have heard from Eric Weintraub, we have also started to use it in VSD.
A couple of the issues, I think access to charts has been brought up several times today. That is an issue in terms of the time and expense to review charts. I think this PEPR approach is an interesting way to try to get around that or to minimize the need for chart reviews.
Another issue is data lags. I think this is a big issue for a priority of preparedness in influenza and pandemic response. I think it is very difficult in the time frame of even seasonal influenza, vaccination, or in a pandemic, to be able to provide timely actionable data, even in VSD where we are able to have data available on a weekly basis, which has lags on the order of a week or a bit more.
During the flu season, most of the flu is given in October and November, and some conditions, like GBS, they take several weeks before they manifest. It's very difficult to identify an important signal that you might want to use to impact policy within that short time frame.
I guess that will segue into the question about the PRISM priority areas. Certainly, I think the area of vaccine adverse events, signal refinement, evaluation. Those are definitely important areas. Take the signal refinement, you're on your way of doing that.

Evaluation, yes, that is something to strive for. You need protocol based assessments, and they can take a long time to do.

Your signal detection methods, again, I'll go back to TreeScan, and I think that may be one of the more valuable features of PRISM. Again, the issue, as I mentioned, about influenza and pandemic response, the data lags. I don't know how feasible this is, given current data lags, if something can't be done to shorten that. Even if you could make it very short, it's still hard for influenza vaccine to be able to do that in a really timely manner.

I think the other priority area of vaccine safety is in pregnancy. I think that is a big priority area in vaccine safety nowadays. I think in VSD we found it important to be able to link with state birth certificates to be able to get accurate start and stop dates of pregnancies, which has been important.

I think some issues are more amenable to automated analyses than others, like things such as prematurity, low birth weight, small for gestational age. I think we have even published studies where we have developed fairly reasonable algorithms for major structural birth defects, and to be able to do that.

Conditions such as spontaneous abortion and stillbirths may be more difficult, particularly if you are not able to link to birth certificates or to medical charts. Spontaneous abortion in particular has issues that the early spontaneous abortions may not even come to medical attention, and getting a gestational age is difficult, and we often need to go to charts and get ultrasound to be able to do that. For stillbirths, also obtaining the gestational age at the time of stillbirth is a difficult issue.

I'll turn to coordination between VSD and PRISM. I think our goal -- we spend a lot of time interacting with each other to try to the extent possible make sure the two systems compliment, synergize, and do not duplicate effort.

I think there is a potential to utilize both systems in a synergistic fashion in signal detection and verification and evaluation. I think as Eric mentioned, in VSD, in the early years, we stayed away from data mining and signal detection. I think one of the big concerns was VSD was the only system available at the time, so the question was if we identify a signal, where are you going to evaluate that signal. Now, there is another system available.

I think the order, to my mind, looks like it might work would be for PRISM to be the signal detection system because we have a large database. You have the automated data, but then you have the issues of access to charts, which may be more difficult.

VSD could then serve as the verification evaluation step, where we have more ready access to charts, electronic health records, and other ancillary data. I think we may be more able to more quickly implement an assessment.

That said, I think data mining like TreeScan is best for acute onset, serious conditions, that are treated in the emergency room or the hospital, but that leaves open the question of how about conditions with delayed onset or don't come to medical attention, or are treated primarily in the outpatient setting. These are conditions that really a lot of the questions about vaccine safety nowadays kind of circle around, these delayed onset autoimmune

conditions or developmental delays and such, that are primarily seen in the outpatient setting.

DR. ANDERSON: Okay. Time is up. Dr. Seifert?

DR. SEIFERT: Obviously, thanks for inviting us and for sharing this information. We appreciate it and look forward to what is going to happen over the coming years.
I should comment that one of the advantages of going on in the afternoon is that a lot of the questions that I had or concerns that I had have already been aired or been aired and answered. So, yay! I don't want you to think you're completely off the hook. Of course, I still have additional questions. (Laughter) Dr. Destefano already addressed some of them, which is helping us understand conceptually where PRISM sort of fits into the signal detection/signal evaluation picture, at least in the U.S., and beyond that, globally.
Speaking only for myself and not for my employer, I personally am more concerned about how we manage or elucidate signals than figuring out new ways to detect new signals. I sometimes think we are better at detecting them than we are at really resolving them.
So, hopefully as our sophistication and understanding of the resources behind PRISM and health records and that sort of thing evolves, we will get better at that part.
PRISM has been held up as essentially a resource for the agency and for the Federal Government, and one question that we have that I think one of my colleagues will address is whether sponsors or manufacturers or whatever you want to call us can access PRISM, and if so, how would that work in terms of the logistics. Would it be something like VSD where we would have to pay an intermediary, has thought been given to that.
Obviously, the next part of that question is going to be and what is it going to cost. There are economic concerns. On the one hand, supporting the system and helping to keep it healthy and growing has to be balanced with just what dare I say the market will bear. I'm aware I'm sounding very commercial, which would make my commercial colleagues laugh hysterically.
I still, I think, would appreciate a better understanding of what the regulatory obligations and implications of findings in PRISM, especially in terms of signal detection would be. I don't have a really clear understanding of that. I suspect the answer is going to be well, it depends, which is fine, but understanding where this fits in would be helpful.
For example, will an isolated finding in PRISM necessarily have to wind up in the U.S. label?
The last two questions, I think, are the harder ones, which one is you have spoken a bit about, how do you validate these both in terms of other datasets and in terms of digging down into these data. I think that's important.
The question of whether findings from PRISM would have to be replicated or reproduced. I think you have actually addressed that quite nicely.
I think the last piece is, and a lot of us are safety or pharmaco-epi people, we talk about

risks and potential harms, I think we also have to talk about benefit- risk balance, and I'm hopeful that later this afternoon there will be some discussion about using the same type of data to also look at potential benefits, so we can get a more balanced picture.
That said, with a prophylactic interaction, we're going to come back to the issue that you have identified in terms of what I'll call "timeliness," latency of the data appearing, especially for a pandemic or rapidly emerging infectious threat, and how long do you have to follow up for some of the at least hypothetical concerns, there can be a latency of years.
In summary, and I think I have kept to my time, thank you. I think there are a lot of opportunities here. I think it's really exciting, but as always, I think I'm left with more questions than answers, and I suppose that's a good thing.

DR. ANDERSON: All right. Thank you, Harry. Next, is James Stark.

DR. STARK: Thank you. Thank you for inviting me to speak as a panelist. My name is James Stark. I'm an epidemiologist at Pfizer. My comments are going to focus on the partnership with industry, and also utilization for regulatory action.
First, I would like to congratulate CBER and FDA's effort in establishing the Sentinel PRISM system, the stakeholders involved, including the data partners. The coordinating center and CBER have developed and efficient system using established data and new methodologies to conduct high quality vaccine research which improves the public's health.
A partnership is defined as an association of two or more partners. A partner is a person who takes part in an undertaking with another partner where there are shared risks and benefits.
As we listen to the feedback from the stakeholders, a partnership theme has emerged, one with examples of successful partnerships and others that need improvement. So, my simplistic view of PRISM is as follows: priority areas for assessment are defined. Studies are designed. Protocols and final results are posted on the website, and the results are communicated.
So, for each of these steps, we can review how the partnership with industry has performed. As noted by others, including Dr. Destefano, PRISM has many priority areas, but how and with whom those are defined is not clear. I think this is an area where the partnership with industry could be strengthened.
There are instances where industry, including Pfizer, leads in developing new methodologies in assessment, and input into these priority areas could be valuable to all the stakeholders. Thus, I pose the question of is there an opportunity for industry to have a role in defining priority areas?
As noted by Dr. Velicer from Merck, the studies are designed by the PRISM investigators and protocols are posted on a Sentinel website for public comment. In Pfizer's experience, our comments to date have been addressed and taken into account, which is a clear

example of a system and partnership that works well.
One area for concern which could occur, I don't know if it has to date, is if a pharmaceutical company has a major concern about the study objectives or design. In this case, are the benefits and risks shared by PRISM and industry? Would PRISM carry out the study if benefits and risks are not shared? Does a process exist for study mediation?
Finally, as results have been communicated, it has been noted that the conclusions drawn are measured and reflective of the results, and caution in the ability to draw causal conclusions and the need for additional research has been stated, and this has been well received.
My next comment focuses on strategic implications for the future, specifically utilization of PRISM for regulatory action. Utilization for regulatory action can occur in several ways. PRISM has data mining methodologies for single identification, which is an important step. However, this poses numerous challenges. Obviously, there is the opportunity for false-positives.
Furthermore, PRISM as a single identification source presents new questions for a holistic view of pharmacovigilance, and includes information from all phases of development and the importance of interpreting signals in the context of different paradigms.
Each of these mechanisms is resource intensive, and while we cannot make the claim that one source is superior to another source, understanding the role of PRISM is single identification needs to be clarified.
Regulatory action can also occur in the form of a post-marketing commitment study, and the PRISM data sources are unique in their sample sizes and robust in their data fields and linkages. As such, use of these data sources for hypothesis testing studies to support post-marketing commitment studies would be valuable. In fact, Pfizer has engaged the PRISM data sources and set up a coordinating center to conduct a post-marketing commitment study for the FDA.
Later in Session VI, I will present a detailed look at the motivation for the study and how we are going to use PRISM. Thank you, and that concludes my comments.

DR. ANDERSON: Thank you, Dr. Stark. Karen Bok, would you like to go next?

DR. BOK: Yes, sure. Thanks for inviting us. I just want to have a disclaimer. Our comments are going to be very different. We work at kind of a 30,000 feet view, so the things we discuss about the vaccine and safety system in general are more global. You have my permission to eye roll if you want. Maybe sometimes we don't understand the methodology enough to have the right solutions or propose the right changes to the system.
I think first we want to congratulate, like someone said this morning, we have this amazing system going that didn't exist before the 2009 pandemic. It is such an integral part of the vaccine safety system in general. We depend on it so much.
The other thing is I think about three years ago, when I joined NVPO, the main concern

was active signal detection and how that was one of the downsides of the Federal system. I think it is great to see we are already working on that, and not only PRISM but VSD, utilizing technology to implement that.

The rest of my comments, I thought I would tell you about things we discuss at HHS about vaccine safety. You might take those suggestions or not, and if they apply to PRISM. We think about preparing for all the situations or emerging situations, what is going to happen if we have another, will the outcome change, are we going to deal with it better, are we going to be able to predict the vaccine was given at the peak and maybe a schedule change would have prevented that.

That is one of the outcomes that I can use as an example. What about, for instance, narcolepsies? I think someone mentioned today those cases where it's hard, like GVS, to detect them, associated to a vaccine. I know it didn't happen here in the U.S., and it was confirmed that it's probably not a high risk in the rest of the world, but what if it had happened here in the U.S., and how we would have dealt with that, if we are prepared to deal with something like that, that is so rare.

The other things besides vaccinations and vaccine safety during pregnancy, which is a very big priority in our office as well, not only for outcomes that are very common in pregnancy in general, but also congenital outcomes.

We also are thinking about vaccine safety in the elderly because we had an RSV vaccine coming, but unfortunately that is not going to be happening soon, but we have a new Zoster vaccine. We might have a new norovirus vaccine. The elderly field is active, and it is going to have a lot of new vaccines. I know there are unique challenges to starting vaccine safety when there is so many cofounders in a population like that.

Other things we discussed is what happens when we have another pandemic, when another 2009 comes along. I know someone said this morning that you have the capability of linking your records with immunization registries, and how you are going to use that. That is going to be necessary since people get vaccinated not at the usual office visit or not at the usual site, it is usually a pharmacy or supermarket, or even now, I got my flu vaccine for the last 10 years here at NIH or at HHS. I know NIH has an electronic record, they scan my ID. HHS doesn't. I fill out a paper. How to deal with those situations.

I know a lot of that is the immunization registries are very challenging. It depends on the state. It depends if you have also what type of vaccine, Subpart B, Subpart D. There are a lot of other factors that doesn't only involve PRISM, but it is something to think about in how to improve that response in the future.

Other types of situations like another mass campus vaccination for Meningitis B or a vaccine that hasn't been licensed yet, but maybe we don't want to leave it to the manufacturers to track the vaccine safety record.

The other big issue that we have been highlighting a lot in the past months is the vaccine injury compensation program. Because of a new political situation and because the vaccine injury compensation program is about to be 30 years old next year, and it was

designed 30 years ago, it is facing a lot of new scrutiny. It is a little bit outdated, it could be changed.
I think it is also true what Dr. Marks said, now we live in a time where assurances about the safety of a vaccine are very important, and the vaccination injury compensation program is our weak spot.
We had a conversation not so long ago about how can we talk about the injury table, and if GVS needs to be analyzed every year, depending on a new flu vaccine, and if that needs to be included on the table or not.
Even talking about injuries that are outside the table, how are those cases settled and can we contribute in any way to clarifying if any of those outcomes were really associated to vaccines or not. I think anything we can do in that arena and collaborating with HRSA will be very helpful.
I think that is all I have. Thank you.

DR. ANDERSON: All right. Thank you. They are giving me the high sign over there and dirty looks.
(Laughter) Bob Davis.

DR. DAVIS: Thank you again for inviting me. This has been an eye opener. Really, I congratulate you on putting together an extremely productive network that is very organized and has a really nice systematic approach to safety evaluations.
My comments are going to be a little bit granular because they are just reacting to -- I don't have any set agenda. I'm just reacting to what I've seen today.
One of the things that you haven't talked that much about and that others have mentioned is the challenges in getting more current or recent data, more timely data. That is probably going to be a big challenge.
You're probably going to have to really carve out specific approaches to certain participating health plans who can give you direct data, where that data will sort of go in a different pathway than through the typical health plan setting. If you want to get it in a more timely fashion, within 24-48 hours, you will have to get it in a much dirtier fashion where it hasn't been cleaned, it hasn't been validated, but it is there.
Frankly, from my point of view, there is usually too much attention paid to validating it when you're looking at just active surveillance. You can actually deal with dirty data on the other end, but it will require probably some real politicking to get access to that kind of data.
On another issue, there hasn't been much discussion of systematic evaluations of the positive predictive value of the codes themselves that are used. I know this has been done sort of helter-skelter in the past, and this might be helpful in the future, which is you could create a systematic approach to evaluating the predictive values of certain ICD-9 codes or you could even model, like what is the predictive value of febrile seizures, what is the

predictive value of febrile seizures in emergency departments, what is the predictive value of febrile seizures, people who are placed on antiepileptic's or diagnosed by a specialist. This is sort of similar to what is being done in other networks, like the Emerge Network, and you might want to consider doing it here in a systematic fashion if it's not already being done.

This could also be aided by the analysis of text data. There is a whole world of data science that now centers on extracting data from text data, from doctors, nurses, social workers' notes, and the like, or from image data. Those could also be used to phenotype your data.

There is also obviously the interest in getting access to inpatient data, so you could look at the safety of vaccines given in the inpatient setting, or to just get more information from what happens in the inpatient setting.

We have some experience, and it is quite interesting what is being collected now. You can get lab data, most of this data is time stamped, so it is actually quite useful to use to get an idea of the medications and vaccines given in the hospital, and those could be integrated into your studies as well.

Some other comments. I think some of the previous speakers have talked about whether or not PRISM can be used to replace or supplement the post-marketing trials that are currently going on at pharma companies. Dr. Seifert and Dr. Stark mentioned this. I'll just note this topic has been sort of danced around now for at least 10 or 15 years. There is a little bit of progress, not as much progress as I think we would all have hoped for. That topic probably needs a leader on both sides of the aisle to really move it forward, actually, all three sides of the aisle, the scientific leaders, the FDA, and pharma, to come to an agreement as to what that means.

Two last comments. One that is sure to raise the hackles of some folks here, which is I want to raise the idea of considering producing the identified public use dataset. The data that is collected and analyzed here is extraordinary, it is wonderful, and it's perfectly designed not to be able to be made into a public use dataset, but those datasets could be very useful for methods development, for junior faculty explorations, for work, for publications, for a whole bunch of additional type of analyses that would actually probably supplement the scientific productivity of what's going on, which is already quite impressive.

Lastly, we have heard a lot about transparency, but we really haven't heard about how priorities are set and how directions are made. Questions that came to my mind, how are you deciding what studies to do? Not necessarily whether that should be the topic of this conversation, but I'm a little bit surprised of the absence of any discussion of that. Is there a vaccine safety plan that is being followed and addressed? Who decides what questions are addressed and in what order?

That said, I would strongly recommend close collaboration with the CDC to make sure their priorities are aligned and synergistic whenever possible with yours, most importantly

to aid in validation of signals from one system to the other.
There are also our friends on the other side of the ocean or both oceans really now, the European colleagues and other foreign colleagues who have similar networks of substantial size that could be used to validate and share information. They could be used for signal generation or signal validation, et cetera. Thank you.

QUESTION AND ANSWER SESSION

DR. ANDERSON: Okay. Thank you so much. I think we are at the question and answer time. I'll open it up first of all to the audience. Do we have any questions for the panelists? I know it's after lunch. Everybody is sinking down in their seats. I thought people were taller this morning. (Laughter) Any questions from the audience?

DR. WILSON: Yes. I'm Jerome Wilson from GSK. Dr. Davis, would you say a little bit more about the use of this dirty data and exactly what is going to be the endpoint of it? We in epidemiology spend a lot of time thinking about cleaning data. I understand your point, but exactly what would we do with it once we have analyzed this dirty data?
DR. DAVIS: I'll probably regret using that term.
(Laughter) So, strictly out of experience based on really one of the very first studies the VSD did that I was intimately involved in, where we analyzed febrile seizures after vaccination, and we had a specific relative risk based on just the automated data.
Then we did literally well over two years of chart review and analyses, et cetera. We came up with a relative risk that wasn't a whole lot different than the estimate from the crude data.
When I was at the CDC, we were able to utilize data that was being collected on a nightly basis, again from the VSD, to look at Guillain-Barre Syndrome. These data were really quite useful in signal identification, trend identification. A lot of times the signals were validated, sometimes they weren't, or many times they weren't.
There is quite a nice benefit of at least knowing what the most recent current data was telling you, and that was usually aided and abetted by your experience in knowing how believable that particular data was.
For example, a diagnosis of heart attack or stroke, there are many studies that show that the positive predictive value of those are well over 85 to 90 percent. Knowing that, if one finds a signal based on that kind of dirty data, one has a certain degree of confidence. Similarly, if you are dealing with a diagnosis that you have never dealt with before, there is a lot more -- well, you move a lot slower, a lot more hemming and hawing, and the need for further investigation before one makes proclamations that sound too certain.
I'm going to let some of my more learned colleagues weigh in here.

DR. SEIFERT: Since I'm one of his less learned colleagues, I'd like to pick it up. I'd like

to sort of expand what Bob was talking about, but just say if we put aside our pharmacoepidemiologist hat and put on our pharmacovigilance hat, I think one of the potential uses of this is a rapid cycle analysis, and we have spoken about that in terms of short latency during times of rapid uptake, such as during perhaps treatment of an outbreak or an emerging infectious threat, such as a pandemic.

I think in that instance -- I understand and I'm especially sensitive to the risk of, if you will, a false- positive signal, but I think the pressure is on at that point in a signal detection activity to look at -- the vernacular would be "big ticket items," and I don't want to trivialize this, but major emerging threats, and I think given the amount of time it takes to clean data and to refine data, I think there is potential benefit to having data that are not cleaned and perfectly validated to do the signal detection activity for these high risk or high impact type events, especially in that circumstance.

I think, not to be speaking for a colleague, that's where you are coming from. That's my concern. I'm not advocating we do this routinely or we do it for signal strengthening or signal validation, but I think there are times when the time pressure is on and the risk to the public is potentially there where perhaps not taking the opportunity to validate everything up front may be justifiable.

DR. WILSON: I think that is understandable in these prescribed events that you expanded on, and that's what I wanted to hear.

DR. ANDERSON: Hector?

DR. IZURIETA: Just trying to make a clarification. We have used dirty data for GBS signaling for a number of years. We used historical controls. It is successful experiment of sorts with lots of false-positives.

I will change the paradigm a little bit, if you let the river flow with the data, that does not mean you checked the data, you check the data as well and as frequently and as thoroughly as you can, but you don't impede the flow of data. I think that is the basic principle.

The second basic principle I really adhere to is right now, we have controlled ways of analyzing -- let's call it "dirty data," although I don't agree with the term, meaning if I use self-control methodologies, the bias will be towards not finding a signal that does exist. It's a conservative way of using -- let's call it "dirty data."

I can elaborate afterwards if somebody wants to discuss it. I think we have an obligation if this is called "signal detection," time is a valuable commodity, and we don't have much of that, and I can give you and you have given examples of that. We should let the flow of data go on, and we use internal comparisons, and strong comparison groups of controls are one of them. I will stop there.

DR. ANDERSON: All right. I think we have to cut the questions off. I think we are

ready for our next session. Is that correct?
I just wanted to thank all the panelists, great comments, great discussion. Sorry we didn't have more time for questions. Thank you so much. (Applause)

Session VI: Potential Applications of PRISM for Vaccine Effectiveness

DR. FORSHEE: I believe I have a few slides that should come up. Good afternoon, everyone. Once again, I'm Rich Forshee. I'm with the Office of Biostatistics and Epidemiology in CBER. I'm really excited about this next session that we are about to start.
As was mentioned in this morning's session, there is some interest in exploring how data such as we have in the Sentinel system can be used to explore benefits as well as potential risks. This session is going to be talking about some of our early experiences with trying to use observational data to get a better understanding of what we are calling "vaccine effectiveness" when we are looking at observational data.
I'm a FDA employee. I don't have any conflicts of interest with what we are discussing today.
I'm just going to make a few introductory remarks to sort of set the stage about why we might be interested in doing this, and why we think it is possible. The first point I want to emphasize is that the reason we might want to study vaccine effectiveness in PRISM or other observational studies is that it may not be possible to estimate vaccine efficacy in randomized control trials in certain situations.
None of what we are going to be talking about in this session is to suggest that vaccine effectiveness studies in observational data are going to be a replacement for randomized control trials. However, there are some times when it may be difficult to get the data from RCTs.
Just a couple of examples to get people thinking about when this might come up. In some situations, it may be unethical to randomize individuals to a placebo. For example, if we think we have some reason to believe that a vaccine is effective and there is a dangerous outbreak going on, it may not be an equipoise for randomization to placebo.
It may not be feasible to conduct an RCT for an emerging infectious disease if that is spreading very rapidly through naïve populations. You would have to have all the infrastructure in place and guess where the net outbreak was going to be in order to be able to have a successful RCT.
For some of the endpoints that we really care about, it may not be feasible to enroll a large enough patient population in order to estimate effectiveness, and this is particularly true for rare but serious outcomes, which is something from a public health perspective that we very much care about.
Those are some of the reasons that we might want to use observational data like PRISM to study vaccine effectiveness.
The next question is is it possible to study it in PRISM. Our short answer is we think so.

We recognize the challenges, but we think we have some preliminary evidence to suggest that we can do it, and we are going to see some detailed examples that explain in more detail why we think we can do it.

A couple of things that we are going to see, we're going to see the results from a pilot study that we did in PRISM. Maria Said is going to be talking about this in a moment. It looked at whether the data elements were available within PRISM in order to conduct these kinds of studies.

We are also going to see an example from another administrative claims data, the Center for Medicare and Medicaid Services' data, where we have had some successful projects that have led to publications of at least relative vaccine effectiveness for some cases, and Dr. Hector Izurieta is going to be discussing, for example, the work we have done on looking at the relative effectiveness of high dose influenza vaccines versus standard dose influenza vaccines on flu cases and hospitalizations.

As I mentioned, we recognize this is a challenge, and some of these are going to be discussed in more detail in the later presentations as well.

One of the things that I've noted in my work on these projects so far is it is a huge challenge in order to find an appropriate comparison group. Because we can't randomize, we know there are threats to validity, and you want to find an appropriate comparison group. Ideally, we would like to compare vaccinated subjects to unvaccinated persons, but there can be a lot of concerns that there are unmeasured differences between the kinds of people who seek out vaccines and the kinds of people who are unvaccinated, and this is something we have to think very carefully about.

Also, because we are dealing with observational data and claims data in particular, we recognize that both exposures and outcomes may be misclassified, which is another methodological hurdle for us to overcome.

There are also a lot of regulatory issues that are going to require some very serious consideration going forward. There are a lot of questions that we need to answer about exactly how data on vaccine effectiveness from observational trials could or should be used, and any regulatory issues that may come up.

I think this is a discussion that we may have in the panel discussion. It is certainly something that requires a lot of additional consideration.

With that, I am going to go ahead and introduce this session's speakers. Dr. Gruber and I are sharing the responsibilities for chairing this session. I am going to be chairing the speaker portion of it, and Dr. Gruber is going to chair the panel session.

As I have alluded to, the two speakers that we are going to have today are Dr. Maria Said. She is a Medical Officer at FDA/CBER. Our second speaker will be Dr. Hector Izurieta. He is a Senior Epidemiologist at CBER in the Office of Biostatistics and Epidemiology.

With that, I will go ahead and invite Maria to come up and give her presentation.

PRISM Vaccine Effectiveness Pilot Project:

DR. SAID: Good afternoon. I'd like to introduce to you today an ongoing project within

the Office of Biostatistics and Epidemiology surrounding the concept of vaccine effectiveness surveillance in Sentinel's PRISM program.

There were a number of reasons why we initiated this project. First, PRISM, which is part of Sentinel, and uses a subset of the Sentinel data partners, is a valuable and rich resource. It has a large number of members from geographically diverse areas, and multiple potentially useful data elements. For example, demographics, outpatient pharmacy dispensing information, and outcome information that can be defined using a single or combination of diagnosis, procedure, or dispensing codes.

Second, we knew that PRISM had already been successfully used for vaccine safety studies. I think you have heard about some of those this morning, studies on influenza and febrile seizures, rotavirus vaccines and intussusception, and the quadrivalent human papillomavirus vaccine and thromboembolism.

The logical question then was if PRISM could be used for vaccine safety studies, why not also for vaccine effectiveness studies. Finally, although randomized control trials provide the level of evidence required for regulatory decision-making within FDA, the observational data within PRISM had the potential to supplement the data from RCTs under certain circumstances.

There are times in which additional data beyond that provided by RCTs would be helpful. In certain situations, an observational study might provide confirmation of effectiveness for vaccines approved under accelerated approval or the "Animal Rule."

Briefly to explain this, unlike for traditional approval which provides direct prelicensure evidence of effectiveness by demonstration of protection against disease or in some cases through use of a scientifically well- established correlate that predicts protection against disease, in the case of accelerated approval and Animal Rule approval, a vaccine might be licensed based on a surrogate endpoint that is reasonably likely to predict clinical benefit, or through the use of animal models.

In both the case of accelerated approval and Animal Rule approval, post-licensure studies are required to verify and describe clinical benefit.

Another gap that PRISM could potentially fill might be in the evaluation of effectiveness in populations that were not specifically looked at in the clinical trials. For example, among a specific sex or age group.

Another place in which observational data might be helpful is if you were looking at a rare outcome or a more specific endpoint, such as severe disease or hospitalizations.

There may be situations, as Rich was pointing out, in which a RCT is not ethical and/or feasible. An example of when this might apply is with a potential Ebola vaccine, in which the sporadic nature of Ebola outbreaks, the essentially public health control measures, and ethics of the situation impact the ability for research to assess vaccine protection against disease.

Finally, there might be times in which an observational study could supplement or confirm a RCT, such as in the case of high dose versus standard dose influenza vaccine, for which a

clinical trial was done and an observational study provided supporting data.
With this rationale in mind, this project, which began in June 2015, sought to address the suitability of using PRISM to estimate vaccine effectiveness.
The project had two primary components. First, to conduct an overview of study designs and methods used in other vaccine effectiveness studies, particularly those done in administrative observational databases, and to test out the database through a use case, which would serve as our initial exploration.
The project included an FDA team and a Harvard team, as well as vaccine experts from around the country.
As we moved through the project, we realized that the question of feasibility needed to be approached from many different angles. First, we needed to ask about the data elements that were or were not available in PRISM. What study populations did it capture or not capture. To what extent could we determine the vaccine exposure.
Outcomes. The outcomes are different for effectiveness as compared to safety. How would we be able to determine outcomes of disease? Would we have access to laboratory data or other diagnostic test results, for example. How well could we understand certain covariates such as demographics or socioeconomic status?
Next, we needed to understand what study designs and statistical adjustment methods would be appropriate within PRISM, which is a large administrative database. We also wanted to understand what tools and assessment methods were already available within Sentinel and PRISM so we could leverage these tools for new purposes.
Finally, through the use of a use case, we sought to actually test out the system so we would have a better practical understanding of what might or might not work.
For our use case, we looked at a study by Hector Izurieta, which you will hear about more about this, published in Lancet Infectious Disease in 2015, which used Medicare data to look retrospectively at the comparative effectiveness of standard dose influenza vaccine compared to high dose influenza vaccine in U.S. residents age 65 years of age and older, from 2012 to 2013.
Our first question was really whether a study that was done in one large administrative database, Medicare, could also be done in another large administrative database, PRISM.
It's important to say here that the goal of this project was not to estimate vaccine effectiveness of the high dose influenza vaccine compared to standard dose influenza vaccine. We did not determine the association between exposure and outcome. Instead, what we thought to do was to explore the availability of data elements that would inform our knowledge of exposures, outcomes, and covariates. Basically, to be able to create a Table 1, like this table, from Dr. Izurieta's paper.
So that you can get a broad flavor of the project, I'll give you some examples of what we discussed within the structure of this project approach. For our first portion, which was data elements, one of our questions was about the nature of the study population within PRISM, and what groups it represented.

One of the strengths of PRISM is undoubtedly its size. The population also has widespread geographic coverage, although different data partners may be regionally focused. In terms of age distribution, because people 65 years of age and older are covered under Medicare, this population is less well representative in PRISM. Also, because the population is limited to an insured population, it may not be representative of those without insurance coverage.

For methods, in which we used literature review and expert input to understand the study designs and adjustment methods that might be useful in PRISM, this table gives an example of the output we are working on, in which we identify study designs that had been used in observational studies in administrative databases, provide a description, assess their applicability to Sentinel, and gather examples from the literature to illustrate their use.

For assessments and tools, the Harvard Sentinel Operations Center has developed over the course of many different studies multiple tools, including preset programming that can be used for potential future vaccine effectiveness studies.

I won't speak about these in particular, and I'll add that there are others not displayed in this graphic, but I'll draw your attention to the cohort ID and descriptive analysis or CIDA tool, at the bottom, which was a tool that we used to explore our use case and provide a descriptive analysis for the exposures, outcomes, and covariates.

For our use case, we were able to obtain information and generate tables to describe the numbers of patients receiving high dose versus standard dose influenza vaccinations, the number of episodes and number of patients who received an influenza diagnosis or pneumonia diagnosis, and patient characteristics, including age, sex, and medical history.

In defining our outcome of influenza, we used more than one definition, and looked not only at the influenza diagnosis by ICD-9 code, but also at different algorithms, such as having received a rapid influenza test followed by Oseltamivir prescribing, or having received a laboratory test and then a few days later having an influenza diagnosis within that time.

Where we are in the project right now, the draft white paper has been completed and revisions are ongoing, and when it is finalized, the white paper will be posted on the website.

There were a number of people who were involved in this project and who will continue to be involved in the project, and I want to make sure to acknowledge everyone. Thank you. (Applause)

DR. FORSHEE: Thank you. Now, I will welcome Dr. Hector Izurieta.

Centers for Medicare and Medicaid Services (CMS) Vaccine Effectiveness Project:

DR. IZURIETA: Thank you. I'm going to present a series of studies that we have performed in collaboration with the Influenza Division at CDC and CMS for a number of years using claims data.

Regardless of the fact that this is a collaborative study, my opinions and whatever I say are my responsibility, so I will have the freedom to say whatever I want. (Laughter)
Basically, the problem we are addressing in observational studies is called "bias." I hope at the end of these conversations, I will convince you of two things. The first one, if an observational study has no bias, that's not an observational study. That is randomized.
The second thing I want to convince you about is please embrace your inner bias because bias can only be resolved with bias, and hopefully I will convince you of that.
The third thing is although I'm going to proudly present all the beautiful things we have done, all the research we have performed with Douglas, with Jill and the group from CDC, Jeff Kelman, with Rich here, all of those studies have huge holes in them and huge limitations. I will not talk about that. I will talk about only the good things we have done.
How to address bias. Basically, our main concern in this type of study, and you can disagree with that, was a selection bias, particularly health seeking behavior and also frailty. We have tried to have people comparable in regard to their health seeking behavior, and also comparable in regard to frailty.
We also would like to have ways to verify that the cohorts are comparable. Maria Said has presented some of those ways, descriptive tables, et cetera. Of course, ways to verify and validate outcomes using a claims database. This is very ambitious and the results are not perfect, but hopefully I will convince you that we have tried.
How do you get rid of selection bias? By creating selection bias. In these particular first set of studies, we used a claims based comparative influenza vaccine effectiveness study, by using the comparator of another vaccine, in this case, a high dose influenza vaccine compared with the standard dose influenza vaccine, you decrease the bias related to the fact that some people that get vaccinated are more health seekers than those people who don't get vaccinated.
In 2009, under accelerated approval, my and Gruber's group approved a vaccine called high dose trivalent influenza vaccine, which contained 60 micrograms in a trivalent vaccine for adults 65 years and older. This was considered high priority given the low response of influenza vaccine among the elderly and the high morbidity and mortality complications, et cetera, for influenza among the elderly. Licensure was supported by superior hemagglutinin antigen responses among the high dose recipients.
The objective of this set of studies was to establish whether the high dose vaccine was more effective in U.S. Medicare beneficiaries than the standard dose vaccine.
You could legitimately ask why are you doing this study when there was a commitment, in fact, a requirement for the manufacturers to do a study. Well, the manufacturers tried to do a study in 2010. They completely failed. There were no outcomes that could be analyzed, and at the time that Douglas and our group started considering the possibility of doing this study, we knew we needed a powerful database that would allow us to go into serious outcomes, which were the ones we were the most concerned with, enough power to

analyze that, and also the capacity to look at multiple systems as well.
We tried to study whether the high dose vaccine was more effective in U.S. Medicare beneficiaries than the standard dose. This was a retrospective cohort study using claims from CMS for CMS beneficiaries, which were not entered into Medicare because of disability, et cetera.
The other bias we created, the other selection bias we created was in regard to frailty, which is we either wanted to study a group of equally frail people or non-frail people. What we decided to require is that the people would be able to walk and get a vaccine at the pharmacy, so we restricted the study to people who received the influenza vaccination at the pharmacy under the assumption that pharmacies do not advise clients in regard to the use of one or the other of the influenza vaccines.
Besides selecting implicitly ambulatory patients, by requiring the people who entered the pharmacy entered the pharmacy in which the other competing comparable vaccine was provided in that pharmacy within a two-week window. We also guaranteed the fact that there was an opportunity to get the other vaccine, and also adjusted implicitly for a number of temporary and different variables regarding influenza. By that implicit adjustment, we improved our study.
We also restricted the analysis to what we call the high influenza, defined by 75 percent or more of biological surveillance data laboratory results from CDC.
The outcomes, we tried to increase the specificity of the outcomes without having to do medical record reviews, so we defined a case as a case that consulted for influenza in the outpatient that was tested with a rapid test which could and should be performed at the office, so results would be viable on the same receipt, and for which there was a dispensing of a neuraminidase inhibitor or Oseltamivir, which should only be used for influenza, not for any other disease.
The other outcome was a primary discharge diagnosis of influenza during the high influenza season. That was defined as an influenza hospitalization case that ended during the study base.
By the way, in comparison with the clinical trials which were performed by the sponsor with more than 30,000 participants, hospitalizations, there was no real power to study hospitalizations in the randomized trial. They found some results for pneumonia, none for hospitalizing influenza, and that was not even attempted, and when they tried to select age groups, the data became very unstable really.
This study had, call it advantages, in regard to the randomized trial, although the validity of the randomized trial is difficult to doubt.
We estimated the relative vaccine effectiveness by comparing outcome rates in beneficiaries during the periods of high influenza.
In summary, we analyzed two seasons, and I would present you the results of the two seasons. The first season data was already published in Lancet. The next season data, which is the mortality study led by David Shay from CDC, is hopefully going to be

published in a few weeks.
We studied more than the median people in each one of the groups for each one of the years, all vaccinated in pharmacies. Because the methodology of comparison would allow us to compare very, very large dataset because its standardized by doing adjustments based on the variability of the dataset. Basically, the standardized mean differences used in this particular case, if they are under.1, will be considered very comparable.
As you can see, in the right lane for the partial list of covariates that we are presenting to you right now, all of them were very, very far from.1. The results for the first season, the 2012-2013 season, show a very interesting and high comparative effectiveness with high dose influenza compared to the standard dose influenza of around 17 percent for outpatient, 22 percent for inpatient, and almost 30 percent for fetal influenza. These results are very comparable to the results from the randomized clinical trials.
You could say well, you have done these, there is no need for you to continue this work, and I hope to convince you that there is an imperative to continue it because otherwise I will have to look for a job elsewhere. (Laughter)
In this case, we analyzed also the 2013-2014 season, which was an H1N1 season, the previous one had been the 2012- 2013 season, in which we found significant effectiveness. In this 2013-2014 season, using the same methodologies, we did not find a significant difference. As I said, this is an observational study, meaning prone to bias.
I cannot be completely certain that these results are completely valid, but this suggests there could be differences in the relative comparative effectiveness of the high dose influenza vaccine in seasons in which -- I use the word "much" which is not appropriate, but the compatibility between the circulating and vaccine strain is relatively high versus the seasons in which that is low.
We don't have a complete explanation for this, and we will continue exploring other seasons, but we believe this difference in results is real, and it means we have to continue investigating other seasons.
The first study we published, we used a pharmacy restriction and we used a particular way to validate cases using a test for influenza, antiviral prescription, et cetera.
Also, in a supplemental analysis of the clinical trials, the manufacturers implicitly confirmed that our data were very compatible with theirs, by saying the data from their randomized studies were very similar, they reaffirmed the results from our study, confirming our prior assumption that our results should be similar to the randomized study was basically satisfied.
We don't have a comparator for the 2013-2014 season. We have the comparator for the 2012-2013 season.
Based on these, I would call, successful experiences, we decided to continue with a number of other projects. What about age? Let's say for the year 2013-2014, there appears to be no significant difference for most outcomes except maybe hospitalization comparing high dose versus standard dose.

What about the very old? Is the high dose still advantageous to use in the very old? Do we have data to analyze that?

Also, a number of publications have raised the question of do studies interfere with the effectiveness of influenza vaccines, so we decided to use the same to address this question using also a comparison of fermented and natural synthetic statins, and also a dose effect. The results of the study are being reviewed right now by the journal, so I'm not authorized to discuss them right now. The study has been completed, but we are still in the writing process.

The other project is the duration of influenza vaccine effectiveness during a given season, a project led by our CDC colleagues. The question there would be with the data we have, can we determine whether the influenza vaccination during a given season is higher near the time of vaccination than when you get six months away or so from time of vaccination.

In this example, just to give you a flavor of our age adjustment study, which is led by Rich Forshee, who is here, we are trying to find out whether the very old are better protected against influenza in regard to the comparative effectiveness of the high dose with the standard dose.

If you can look at these graphs, there is a suggestion in these analyses that people who are very old have a higher comparative effectiveness for high dose compared to standard dose for both hospitalization and also probably death. We are going to address this in the ongoing study on age effects.

Also, statins study, we have already finished the first phase which is finding comparable cohorts, and here is a flavor of it. We are showing on the right-hand side a standardized mean difference. They are basically zero, which is better than most clinical trials, I guess. This is only for variables we can see, so I'm not being completely honest on that.

Outcomes, like prior hospitalizations, prior outpatient visits, et cetera, which is in my opinion a great way to validate whether the two cohorts are comparable in regard to the background risk of respiratory diseases or disease in general, or hospitalizations in general.

I could go on with five or six more tables, but I won't bore you, and will move to the next subject. We are also extremely interested in exploring other analytical approaches. Our pharmacy cohort is not generalizable to the CMS population, so we would like to control for confounding but use approaches that are a little more generalizable.

In this case, we are trying to use natural experiments or instrumental variables in which the selection of patients to be vaccinated with one vaccine or the other are driven not by their risk of complications of influenza but by administrative decisions, in this case, by the providers.

There is a very nice paper by Alex Walker that I encourage you to read on natural experiments on equipoise as well.

On ongoing, there is too much to say. These proposed studies that we have started to explore, we can see here the physician prescription behavior on the left-hand side for a given year, which is season 2013-2014, you will see half the physicians in that particular

year only used the standard dose influenza vaccine, which means probably they didn't have in stock the high dose influenza vaccine.

Can we compare these groups with other groups which have different rates of utilization of the standard or high dose vaccine, including those physicians who have 100 percent use of the high dose vaccine? Well, this is a challenge, and I would encourage anybody interested in the subject to approach me after this session, because this is our next job, if you want.

We would like also to rule out a major confounding, at least to verify whether we have a major confounding. Also, reach a more granular definition of periods of high circulation, not only at the regional level, but at the local level.

In regard to detecting whether the results are comparable, a study that is conditionally approved and accepted for publication, we use what we call falsification endpoints or negative endpoints for analysis, primary analysis, in which we compare vaccinated with unvaccinated, and I would say analysis comparing vaccinated individuals with one vaccine with vaccinated individuals with another vaccine.

These negative endpoints overall cluster around one, but as you can see here, the match was really not as perfect as certainly I would have liked, so more to say about this.

A project of significant interest for our colleagues at CDC, a project they are leading, we are trying to determine whether antivirals can be used to define influenza season with more granularity than the test results.

In summary, maybe I have convinced you that there are successful experiences from the CMS studies that could be used in PRISM effectiveness studies. Effects of vaccines with the same indication comparing two vaccines, for instance. Dose response, high dose and standard dose.

Internally controlled comparisons, duration of effectiveness, effect of age, things we are studying. Self- controlled analyses, as difficult as they are to be implemented in effectiveness studies, if we carefully think about uses of self-controlled studies, as we have for safety, we will be able to implement them.

I have to admit that we have had less success with a number of situations. Health seeking behavior, difference in complication risks in comparison with vaccinated and unvaccinated groups, and observed versus expected. That has been hit and miss in some cases. We are successful in some cases.

When we have small differences as in our 2013-2014 season, our trust in the results diminishes greatly even though we have great comparative studies.

I'd like to thank a number of people, Douglas, and many others. Thank you very much.

(Applause)

DR. FORSHEE: So, at the moment we're just going to have the two speakers at the table. We're going to have five minutes for any questions form audience members, specifically for these two presentations. Then I'm going to turn the chair over the Dr. Gruber for the

panel discussion. And there will be another opportunity at the end of the panel discussion for more questions.
So, any questions from the audience for our two speakers? And please state your name and affiliation.

DR. TIKHONOV: Thank you. My name is Ilia Tikhonov. I'm an epidemiologist advisor. Thank you for your presentations.
I'm wondering, what type of surrogate endpoints -- you mentioned that surrogate endpoints are typically -- may be studied in some clinical trials. So, doing an effect of the study in the context of PRISM can bridge that gap. We also know that PRISM, like any other database, may have limitation in terms of how long the patients, members are followed up. So, what are the typical examples that you have thought through where you can bridge that gap between the surrogate endpoint and the actual endpoint in the vaccine in the population?

DR. SAID: I think that's a good question. I hesitate to name specific vaccines that we would do any observational study for, other than to just say that it's good to have that in the arsenal, to know if there is a vaccine that is approved for which undergoes accelerated approval or animal rule approval. That this may in certain circumstances be one of the tools that we have.
I'm actually going to defer to Dr. Marion Gruber, too, to speak more specifically about situations where we might actually use that.

DR. FORSHEE: But one thing I would just build on with regard to that, we certainly do need to keep in mind that people change health insurance plans and so we don't always have a very long period of time at which we follow the patient. So, I think the data will better support outcomes that we expect to see happening in a reasonable period of time rather than something that would be a very delayed endpoint that we would look at. So, that is one consideration.

DR. IZURIETA: I'd like to complement to the response first. For instance, in HPV vaccines we cannot really wait until cancer occurs then 20 years later. So, CIN is a surrogate endpoint. I also use the terms surrogate endpoint a little laxer because when I say I am analyzing somebody who was tested for influenza in a rapid test, which is not sufficiently specific or sensitive, by a physician who believed the patient had influenza and who proved that belief, I think, by treating the patient with a specific treatment for influenza, I would still call that the surrogate endpoint because it's not a PCR confirmed influenza case. Same for mortality. When we use mortality within 30 days after influenza hospitalization, I am assuming -- and this assumption is not completely correct -- that the cause of mortality was in part at least influenza. Some of them will not

be influenza but the bias would be towards -- and if I know where the bias comes from --

DR. FORSHEE: So, Hector, I want to make sure we get a chance for one more question from the audience. We are rapidly running out of time. Right here.

DR. WANG: (Inaudible) Long Wang from Merck. So, this question is for Dr. Said. So, thanks for summarizing the five different scenarios exactly. (inaudible) can be conducted in PRISM. Could you just comment -- once you conduct this type of exit study, (inaudible) studies, what will the Agency do to utilize the (inaudible) regulatory decisions?

DR. FORSHEE: I think the question about how it's going to be used for regulatory decisions -- there will be some discussion of that on the panel, I expect. And I think it would be better to address that there.

DR. WANG: All right. Thank you.

DR. FORSHEE: So, I guess we have time for one more question. I think I saw Martin's hand.

DR. KULLDORFF: So, influenza is a very common disease. Most of the medivac scenes are given for rare diseases that don't happen very often anymore like Percusses or the childhood diseases. So, would the PRISM project be a strength for those types of effectiveness studies? Because the key difficulty there, I think, is finding people who actually got the disease. Considering the sample size of PRISM, which is very large, would that sort of be an advantage of PRISM to find as many of those individuals who had those diseases as possible to do the vaccine effectiveness study?

DR. SAID: One of the things that we talked about within our group was really how our effectiveness studies differ from safety studies. One of the things that came up was your outcome is different and in general a lot of your effectiveness outcomes are going to be more common than many of your safety outcomes. I think that, yes, in PRISM one of the great advantages is the size. And for those outcomes -- those effectiveness outcomes that are rarer such as one of the rarer diseases that I think we would very much see PRISM as offering a good advantage here.

DR. FORSHEE: We're going to have to take a pause on questions from the audience in order to have the panel discussion. I'm going to turn the chair over to Dr. Gruber at this point and we'll invite the panel members to come to the table.

Panel Discussion:

DR. GRUBER: So, good afternoon. My name is Marion Gruber, I'm the Director of the Office of Vaccines at CBER. I would like to welcome you to the panel discussion on the potential application of PRISM to valuate vaccine effectiveness. I think the panel members have taken their places. I was informed that one of the panel members, Joe Selby, from the Patient-Centered Outcomes Research Institute, PCORI, could not make it here in person, but I believe he has joined us on the phone.

DR. SELBY: I'm here. I hope you can hear me.

DR. GRUBER: Yes, we can hear you but it was a little muffled.

DR. SELBY: Is that better?

DR. GRUBER: Yes, that is better. At least I can hear you much better.
So, what I think we will do is first let the panel members introduce themselves because some of them I met here myself for the very first time. So, Joe, if this is okay with you, we're going to start with the panel members in the room and then we will conclude with you. I'll give you a cue. Then what we'll do is give every panel member to make their remarks, starting with Joe. And I think I will conclude the remarks session. Then hopefully we'll have a little bit of time for questions and answers. I believe we have a couple of questions even to guide the discussions, but we'll see how much time we have. So, maybe we can start on the far right with the introductions.

DR. DAVIS: Bob Davis from the University of Tennessee.

DR. SADDIER: Patricia Saddier from Merck, from pharmacoepidemiology department.

DR. FERDINANDS: I'm Jill Ferdinands from the Centers for Disease Control.

DR. FORSHEE: Rich Forshee, FDA CBER.

DR. IZURIETA: Hector Izurieta, FDA CBER.

DR. SAID: Maria Said, FDA CBER.

DR. GRUBER: And then we have Joe Selby from the Patient-Centered Outcomes Research Institute on the phone.
So, Joe, can I ask you to give us your perspective and your viewpoint on the topic of potential applications of PRISM to evaluate vaccine effectiveness?

DR. SELBY: Yes. Thank you, very much, Dr. Gruber. And hello everyone. I apologize I got tangled up between two FDA related events and I have to be at one of personalized medicine down here in D.C. So, that's why I'm calling you by phone.

I'll just preface what I say with the comment that it's a lot of fun talking about observational data and their utility for effectiveness studies. We do it all the time here. The truths are pretty well known, that sometimes they're helpful and they're complementary. They are only very rarely so definitive that you wouldn't want to back it up with a trial. But they also apply nicely to some populations that you can't get in a trial. And while you sacrifice sometimes your total confidence in avoiding confounding, you sometimes face new concerns in biases, like Dr. Izurieta said. New biases that come from not having reached the broad general population.

So, at PCORI we're particularly in effectiveness as opposed to efficacy even, and so we are drawn to data from real world populations. We're very interested in subgroups, subgroup analyses and possible differences in effectiveness in subgroups. We're interested in rare diseases and sometimes rare outcomes. All of which cause for very large populations and observational data give you that.

At the same time, we are trying to do effectiveness, and maybe even worse, comparative effectiveness research where the effects size we're looking for is small. So, if you think about true blood pressure reduction drugs and whether one of them is better for the other for preventing a heart attack or stroke, you know you're not talking about a having of the risk in one versus the other. You know from basic epidemiology that the effects size is not at least the sizes of two, either a doubling or having of risk, you really are worried about confounding.

Vaccines may sometimes have an advantage here because the effects sizes in vaccination at least, one vaccine versus another may be larger than the typical effects sizes sought in other areas in clinical research.

In Dr. Izurieta's example, this was in fact a comparative effectiveness study. So, there point is the effects size was estimated to probably not be huge -- it would have been expected, I think, to not have been huge. Not to be many more than a doubling of the benefits.

A critical question though is in all cases why did some people get a double dose and some people get a single dose of a vaccine back in 2012-2013. That's the issue of self-selection or confounding.

Now, Sentinel and PRISM are world class safety research network, in part because safety signals usually are larger, they're usually more than the doubling of effects. So, most safety signals are larger. And there is less concern about confounding in the typical safety analysis then there is the effectiveness analysis. We give drugs based on who the patient is and based on the disease we're trying to prevent. And that makes the confounding for effectiveness typically worse.

In that regard, it does have to be noted that Sentinel is a database of claims data. It lacks

some of the other clinical data that are now collected in real world settings but don't make their way to claims data. So, for example, in Dr. Izurieta's study, in the outpatient case he wasn't able to say was the influenza test positive, he had to go by a different route, was an influenza test built and did the person receive a prescription for Oseltamivir. You can imagine that some people might have had a positive test and not gotten the Tamiflu and that others may have gotten the Tamiflu in anticipation of a positive test that never came.
So, when PCORI set up a very large national level network to do comparative effectiveness research we didn't go directly to Sentinel. It's set up in an electronic-based record network called CORENET. And I would just, in closing, offer that to do world class effectiveness research we may sometimes need more data that can be found in claims to make sure that the people that get one dose versus another, or the people that do get a vaccination and those who don't, don't differ in ways that influence the outcomes on the basis of the presence of a particular disease versus its absence, the severity of a disease, which cannot necessarily be found in claims but could be found in the EMR, or possible links between the dose given and the likelihood of getting a test that could then be required for the outcome.
So, the bottom line is effectiveness research is more difficult than safety research with observational data. Nonetheless, it's got to be done. We believe it can be done in at least complements, randomized trial evidence. But we can enrich the evidence that is found in claims data. We absolutely need the evidence in claims data. And also, claims and databases like Sentinel create sampling frames in populations that you can confidently follow forward in time until membership lags, for example.
But they have the disadvantages which are all set, to some extent, by partnering them, by linking them with EMR data. In the CORENET and at PCORI for observational comparative effectiveness studies, vaccine or otherwise, we think that a network that has access to both EMR data and claims data, like PRISM, is very often the optimal case.
The last thing I'll say is this: undoubtedly in some cases you can convince yourself in advance, rightly, that the data that are available in claims are sufficiently rich to both make judgments about the comparability of populations being compared and to capture the outcomes.
So, I'll stop there, thank you very much.

DR. GRUBER: Thank you very much. Robert, can I ask you to go next please?

DR. DAVIS: I actually have very little to add in addition to what Joe just outlined. As a matter of fact, the major question that I've been asking myself when I was sitting in the back of the room was why does this seem like it's a question that we're grappling with? I think doing vaccine effectiveness studies in these sorts of databases are complementary. There is simply no one study design that addresses all questions from all points of view and comes up with an airtight case as to what the answer is. So, I think that doing vaccine

effectiveness studies in systems like PRISM or elsewhere are certainly acceptable to explore and to proceed with.

As Joe had mentioned, and I think as Hector had also mentioned earlier, they improve on RCTs in some particular aspects whereas RCTs are really the gold standard in eliminating bias and other sources of errors in studies. Doing such vaccine effectiveness work here in PRISM gives a real-world demonstration of the impact as opposed to randomized clinical trials.

Randomized clinical trials, as everyone here knows, tend to be limited to people who are the healthiest slice and highly compliant, they have time to participate in randomized clinical trials. And I see one of those people about once every three or four months, and everybody else we have to look at vaccine effectiveness in such real-world situations as we have here. These systems can also look at vaccine efficacy in specific subgroups. Hector had a wonderful example of, I think it was Zoster, of vaccine effectiveness in the elderly. The strengths that you have at your hands or your fingertips, you can do propensity score adjustment which actually wasn't discussed that much but is worth pointing out. It used to be cutting edge, now it's pretty much a standard approach to ameliorating the differences between, say, for example, in this case, people who got high dose versus standard dose flu vaccines. One thing that hasn't been pointed out is that those propensity scores I think we can really do a better job than we have done in the past. Sometimes people have claimed to do propensity score adjustments for severity when in fact they haven't taken the full advantage of the wealth of the observational data, the full breadth of the data that's collected, but instead limited themselves to just a couple diagnostic categories. Also, the duration of enrollment can also be incorporated to propensity score adjustments. It makes those adjustments even stronger.

One thing I will point out, it is hard for me to publicly say that these sorts of studies no longer need IRB approval. Maybe that wasn't proposed here, but these are real scientific studies. There is a public health mandate to do this, I agree. But I wouldn't want to be the person saying that IRB approval is too much of a burden to do these sorts of studies.

One last thing that I'll point out is that -- it's probably obvious -- in addition to doing vaccine effectiveness studies, cost benefit studies might be of interest to the health plan partners and return data that is of particular interest to them to show how much money they could save by increasing vaccination coverage in their particular health plan.

Thank you.

DR. GRUBER: Thank you very much. Patricia?

DR. SADDIER: First, thank you very much for the opportunity to provide the feedback in this workshop on PRISM. It's a very productive and very interesting workshop that really nicely summarizes where we are and to discuss next steps. I would tend to agree with Dr. Davis that really vaccine effectiveness is one of the natural next steps for PRISM. I guess

for me the question is not whether PRISM should be (inaudible) effectiveness, but how to ensure that it does the highest quality study.

The challenges that were outlined in both presentations are no different than from the usual challenges that you have with observational studies in general. And to be provocative I would say they are no different from the challenges for safety studies. In general -- I'll go into more detail about that -- but the validity of exposure, the validity of the outcome is exactly the same issue for both. Maybe the choice of a comparison group is a little more challenging for effectiveness.

The issue of confounding bias. I think, somehow, we are lucky with acute outcomes that self-comparison designs kind of take care of most of it, but once you try to tackle other outcomes that are not acute you actually struggle with the exact same issues of trying to adjust for confounding and biases.

Going back to some of the validity issues for exposure, I think for manufacturers who one of the important aspects is to be able to distinguish different vaccines that may have the same generic name, like HPV vaccines. And importantly, also, for effectiveness is the number of doses which we found to be a challenge in claims databases, not always accurate. That would be important to look at very carefully and validate, especially if you are looking at comparing the effectiveness of a two-dose regimen, or a three- dose regimen.

For the outcome, again, it's no different than from safety. Maybe what's specific for some of the diseases that we're looking at in terms of outcomes is that they typically require lab tests for confirmation. And in claims databases and HER databases you typically know whether the test was performed but not the result of the test. So, that's where the limitations of claims databases come from. So, you have to come up with an algorithm basically to look at what combination of cause or procedures and cause, or treatment like we've seen were used for the flu vaccine may give you a high positive predictive value of the outcome. But that's not insurmountable. I think that's feasible.

So, we discussed the confounding effects, the impacts, and the choice of the comparison group I think is definitely a challenge, but, again, no different from what you typically have.

The biggest challenge I feel is with the quality in general of claims data and administrative database data versus EHR data. So, if there was a way to supplement the actual current databases that are used in PRISM with HER data that would be really helpful I think. The other challenge that is seen more often with claims databases, the have high turnover that has been alluded to, and the fact that after there is such a lot of people over time that it is impossible to use this database to look at long-term duration of protection. So, as has been mentioned, you can only look at short-term effectiveness.

In terms of how you can use this information, this real-world data, as mentioned, is really helpful in extending the information to groups that were not included in clinical trials. They're usually extremely powerful and allow you to confound the efficacy of the vaccine to people in different age groups, in both genders, in minorities that have usually not been

included sufficiently in trials, as well as people who are sometimes contraindicated for the vaccine and happen to use the vaccine as is sometimes the case with live virus vaccines, contraindicated in immune compromised people. But these people are also at increased risk of having the outcome and typically take the vaccine. It's one way of looking at efficacy in this group.

We've already discussed the use of these data in terms of showing effectiveness in vaccines that have been licensed only based on immunogenicity data or animal role data. I think they could be used also for comparative effectiveness for a vaccine that has, for example, licensed on immunogenicity as a comparison to an existing vaccine like a PCV vaccine where you couldn't do a trial, actually, to look at efficacy. Even a very large one.

Then, I think, the last point would be -- and it has been mentioned for safety as well as to the ability to do almost real time effectiveness assessment in conditions of outbreak or even for the flu vaccine. Outbreak -- I'm thinking of meneg outbreak, or Ebola, or a rapidly spreading disease like Zika, to look at the effectiveness of a new vaccine that is being used in a new situation. So, there are many ways I think PRISM could be used to learn more about the efficacy or effectiveness of the vaccines.

DR. GRUBER: Thank you so much. We have Jill going next.

DR. FERDINANDS: Thank you very much for having me here. I think a lot of what I was going to say has been touched on by the other speakers but I'll add a few things.

I have been in the influenza division at CDC for about ten years now, and I was there working on influence of vaccine effectiveness studies before the pandemic and then during the pandemic, which was a whole different challenge, and then since the pandemic. IRB is definitely a concern; we can't get away from it. And we realized that these data sets have tremendous value, particularly in terms of their size and the ability to look at rare outcomes.

We also want to be able to leverage those, to look at vaccine effectiveness, but we do have sort of a cautionary tale from the influenza history. That is, in the late 1990s and early 2000s there were a series of studies that looked at the effectiveness of influenza vaccines against mortality outcomes in older adults. You guys probably know this story, but these studies came up with a very high level of vaccine effectiveness against mortality, in fact so high that some people really shook their heads and said this is implausible, too good to be true. And, yes, in fact it pretty much turned out too good to be true.

Now, it is widely believed and persuasively so in my opinion, that those rosy estimates of the vaccine effectiveness were largely due to bias and not to true vaccine effect. So, that's sort of the bad news. Those data sets -- the bottom line is they didn't really have the richness of the clinical data that we needed to control for the confounding to get rid of the bias. So, that was disappointing.

But the good news is that that really was a motivation to derive some novel study designs to

look at influenza vaccine effectiveness. Specifically, we have at CDC since the pandemic really built up some networks of investigators that do annual assessments of influenza vaccine effectiveness both in the outpatient setting and now more recently in the past two years in the inpatient setting. These networks use a different design, a different system, which we tend to call the Test Negative Design. It was intentionally designed to try to control of the bias related to health-seeking behavior that vaccinees seek healthcare more readily than non-vaccinees, among the other differences between those two groups.
It's essentially a case control study where everybody who comes in with acute respiratory infections tested for flu and the cases are those who test positive and the controls are those who test negative. So, it relies on a lab-confirmed outcome which we have found to be particularly important and one of the shortcomings that is challenging to address with a data set like PRISM.
I will note, however, that in our vaccine effectiveness studies that use this design, we have recently, actually, come back to using a lot of larger data sets and EMR data sets to augment what we collect. So, it really has kind of moved towards a combination of sources. I will say that I think which data the administrative data sets can offer in terms of looking at vaccine effectiveness and doing so without a huge risk of bias -- there is always some risk of bias -- depends a lot on the pathogen, it depends on the vaccine, and it depends on a lot of very specific contextual factors. So, when you look at a lab-confirmed outcome, for instance, you will have different sources of bias to be concerned about than you would if you were looking at a more non-specific outcome.
So, I think it's a mixture of advantages and challenges. I do think effectiveness probably can be looked at. It's going to be tricky looking at an unvaccinated comparison group, both from the confounding perspective that we've talked a lot about, but also from just classification of exposure. I mean, we know that for flu vaccine at least it's hard to get billing data on all the people who are vaccinated. So, we know there are gaps.
And from a vaccine effectiveness, a methodologic perspective, we really are plagued by the fact that VE as a measure is very, very sensitive to small changes in relative proportions. So, you don't need big absolutely differences in characteristics to have a noticeable significant bias. You need only small relative differences to influence your VE.

DR. GRUBER: I think we are almost out of time.

DR. FERDINANDS: No, no, that's fine.

DR. GRUBER: Thank you very much. I, last but not least, was asked to give the regulatory perspectives and some regulatory considerations, and perhaps to get at the question on what the thinking is on news of effectiveness studies in regulatory decision-making. A couple of things that I wanted to highlight, which have been already

touched on in this very session, and just perhaps go into a bit more detail. When we give a labeled indication, if we put an indication statement into a package insert, we have to have data and there has to be data there that demonstrate a substantial evidence of effectiveness. Now, what is that? That's a term out of our regulations. It really means that we need adequate and well- controlled studies to demonstrate the efficacy of a vaccine. We've heard that we have other licensure pathways, they were briefly reviewed by Maria. We can approve vaccines under accelerated approval conditions. Usually that is an antibody title that we use as a marker that is reasonably likely to predict benefit. And then the vaccine money factor has to confirm the clinical benefit by doing usually clinical disease endpoint studies. In some cases, if we have well-established correlates of protections, it is possible to give approval based on the surrogate. Example, hepatitis B vaccines and antibody titles.

So, I would like to stress that even in recent times we have many examples and cases where it is possible to do randomized controlled clinical studies and clinical disease endpoint studies to demonstrate the efficacy of a vaccine, or to confirm the clinical benefit of a vaccine. To reiterate what Hector said, the regulatory background of the flus on high dose approval, that was an accelerated approval based on an antibody title.

But the vaccine manufacturer then did confirm the clinical benefit by performing a randomized control clinical endpoint efficacy study that was mentioned before. And then, of course, the study conducted by Hector and colleagues really confirmed and reaffirmed the findings of that study.

That being said, FDA, the Agency does recognize that there are situations like those that have been mentioned, you know, outbreak situations of emerging infectious diseases or situations where the disease incident is just too low to do a clinical disease endpoint and randomized clinical trial. Or the situations where we already have a licensed vaccine that is recommended for use and for which a sponsor may seek an additional indication.

All of these are situations where it may either not be ethical or feasible to do a randomized controlled clinical trial. And in these situations we would consider observational study, perhaps even including studies conducted in PRISM, to really demonstrate the effectiveness of the product. So, there are certain scenarios in which we consider alternate approaches.

Again, of course, we would have to look at the study design, the need to be prospectively designed, incorporate approaches to limit bias, as was pointed out here repeatedly. And, of course, we need to look at product-specific effects so that we cannot really rely on class effects.

We have taken these considerations to a public discussion. We convened a raw pack about a year ago where we actually discussed observational studies to label the Tdap vaccine that are the combination TD and pertussis vaccines that are already licensed and that are recommended by ACRP to be used in pregnancy. So, there a sponsor approach does really get an indication in the package insert that would stage a prevention of pertussis

disease in the newborn infant.
So, it would not be possible to do randomized clinical trials in these situations, not ethical, because the vaccine is already recommended in the United States for use in pregnant women. So, in these situations we have discussed the use of observational studies to really demonstrate vaccine effectiveness. So, that is one example.
Now, again, I would like to stress what Richard mentioned at the beginning of this discussion, that these studies are really not to replace randomized controlled clinical trials. So, it's not an approach to be broadly applied in situations where randomized controlled clinical trials can be conducted, but it is really an approach and a path forward in those situations where it is not feasible to do randomized controlled clinical trials.
With that, I think we can conclude our remarks. I can see we have about five minutes left. I think at this point I should really invite questions from the audience. Thank you.
(Applause)

DR. GRUBER: Do we have any questions? I see a hand in the back, yes?

DR. ROCKHOLD: Thank you. Frank Rockhold, Duke University. I just want to follow up on some of the comments Joe made about the electronic health records, and I think the depth of information. And I guess make a friendly amendment to something that Dr. Davis said. In a typical clinical trial, it is true you're only going to get patients who want to be compliant, but in a pragmatic trial where there is no -- compliance is not an issue. You're banking there's very few inclusion/exclusion criteria. So, by using the electronic health record system and doing a pragmatic trial you actually eliminate a lot of that compliance issue because the follow up is built into their healthcare.
While I agree that that's true in a quote unquote normal trial, pragmatic trials I think do have that advantage. I think those would be something to be considered for vaccines.

DR. GRUBER: Thank you. Any additional comments?

DR. SALMON: Dan Salmon, Johns Hopkins. While we're picking on Bob, I thought I would also just at least ask a question or raise and issue about the issue of IRB review. I'm sure there are others here that are more up to date than I on this issue. But when the PRISM project was first put together OHRP looked at it and said this does not require an IRB review. And the rationale within the office was not consistent. But what was consistent was that it wasn't necessary to go through an IRB.
So, perhaps that issue has changed. Bob, maybe you want to elaborate on what you meant a little more. But I think that at least in a situation like we were in 2009, it would have been impossible to do what was done if we had to go through IRBs.

DR. DAVIS: Perhaps I should clarify what I was alluding to because actually I agree with

what Dr. Ferdinands had said and what you just alluded to. In specific situations, obviously, IRB would be -- the approval to move forward with an IRB review is perfectly understandable, acceptable, and I agree with it wholeheartedly. I'm not suggesting any changes needed to the way that PRISM is currently going, that IRB is not needed for these routine safety surveillances of either vaccines or in the context of Sentinel initiative for drug safety. What I'm talking about here is a very careful multiyear study done on vaccine effectiveness that occurs outside of an epidemic or emergency situation where people have, in essence, the time to sit down and develop a protocol to have multiple looks at the data where the data already exists.

To me, there is no obvious difference between what, say, for example, what Hector did and, say, as I do. And I would love not to have to get IRB approval, don't get me wrong. It's the bane of my existence. But at some point, it seems like we're going down a slippery slope and I think we just have to be honest about that and just say that there are times where this is just, in essence, a regular study and we should get regular IRB approval for that. That's all I was saying.

DR. FORSHEE: Thank you very much for that. I wanted to just follow up a little on this. The studies that Hector was discussing were not conducted under the Sentinel framework. The studies that Hector was discussing were projects that we did in collaboration with CMS and CDC. And they did have IRB review. I believe that they were found to be exempt after the IRB review. But the vaccine effectiveness studies done in CMS discussed by Hector did go through our normal IRB process.

I think there is a broader question with regard to Sentinel and that is Sentinel starts to think about doing VE studies, but I did just want to be clear about that distinction.

DR. GRUBER: Go ahead.

DR. WANG: This is for Dr. Gruber. Since first summarizing the Agency's current thinking on the use of the effectiveness data itself, I don't agree this shouldn't be intended to replace the efficacy studies, particularly when randomized controlled studies are feasible. So, I was particularly interested in hearing your thoughts on the scenario that says this is a randomized controlled study conducted, but a lot of times manufacturers will request to do (inaudible) commitment or requirement to do long-term follow up effectiveness data. And I'd like to hear your thoughts on how those data can be used, whether that can be used for the label. That's one question.

The second question is you mentioned about indication expansion. Could you further articulate, say, if there is an indication of (inaudible) maybe manufacturer is looking to expanding to other indications. In that particular scenario, is the Agency's thinking that effectiveness can be used in place of efficacy study or still randomized controlled study? Is efficacy study preferred?

DR. GRUBER: If there is already a labeled indication and the money factor is seeking an additional indication that would be -- again, the consideration is, is it possible to do randomized controlled clinical trials? And if it is possible to do so in order to gain an additional indication then our RCT should be conducted.
So, again, we would really have to consider is it feasible, is it possible to do this clinical endpoint randomized clinical trial? If not, we would consider other approaches.
And I don't know if I really quite understood your first question, but maybe one of my colleagues did? Could you repeat that? Yes. And I wondered if it was more pharmacovigilance, but please, we need clarification.

DR. WANG: Sure, I'm more than happy to clarify that. The first question is regarding a scenario that if a vaccine is approved already but the manufacturer has asked to conduct a long-term effectiveness study, and how that information can be used in the label. Or whether that can be added to the label.

DR. GRUBER: Have we asked manufacturers to conduct long-term effectiveness studies? I'm sort of thinking. Hector, do you want to comment on that? Help me out here. Thank you.

DR. IZURIETA: I don't know if it's required but I will give you two examples for Herpes Zoster. The long-term effectiveness has been questioned. So, the manufacturers did supplemental studies which were initiated based on the randomized clinical trials. These studies are no longer -- the long-term studies are certainly no longer considered a clinical trial, but it was performed by the manufacturers with the express intention of determining long-term effectiveness.
Your example with when HPV was licensed, of course, we used a surrogate endpoint CIN but we really wanted to know whether the vaccine really effectively worked against cancer. So, supplemental studies were performed in northern countries. I don't know if it was required, but I think it was required by us, right Marion?

DR. ANDERSON: I think the question was did the information ultimately end up in the label. I don't -- we don't recall that it did.

DR. GRUBER: The answer to that is no. But I think if I understood your question correctly, it was would we even entertain putting such information in the label. And I think we would be open to discussing that with the vaccine manufacturer. So, that's as far as I would go at this point.
I see that we have one minute left. So, if there is another comment -- Joe, you are still on the phone. We don't want to forget you. Is there any comment that you have for us?

Okay. Go ahead, Joe. We need to have Joe's microphone open please. Joe, I don't think we can hear you, so. Can you hear us? If he doesn't hear us, then he cannot answer. I am sorry. I really wanted to give him a chance to make a comment. Now, I see the red line is blinking.
So, I thank you very much for coming to this session. And I thank the panel members. I think it's time for a break at this point, thank you.

DR. OBIDI: Just so we can keep to our time, this break is going to be ten minutes. So, be back at 3:45.
(Recess)

Session VII: How can PRISM be utilized by other stakeholders?

DR. PLATT: Thanks for many of your for sticking with this last session. The session is entitled How Can PRISM be Utilized by Other Stakeholders. So, by way of introduction, I want to sort of make sure that there is unanimous consent about the notion that PRISM should be used by other stakeholders.
This is an example. You can see from the slide that it's a 2007 slide of what life was like before there was a system like Sentinel. So, this is a true-life example of a first meningococcal vaccine, Menactra. The concern that very soon after the vaccine was licensed, and ACIP recommended that the adolescents receive it, that there was a nontrivial number of spontaneous reports of Guillain-Barre syndrome. So, there ensued an enormous number of questions about whether the vaccine was safe, and if it wasn't safe how risky was it, and was there a high-risk subgroup.
We were in middle of a mix or organizations that put together a post-marketing surveillance study. This is the publication of that study, Risk of Guillain-Barre Syndrome after Meningococcal Vaccine. On the fly, we participated in and helped assemble a coalition of five health plans that had
million members. There were about 13 million people who were in the appropriate age group. There were 1.4 million immunizations.
We actually identified and confirmed all the Guillain-Barre syndrome cases in that ten-year age window over the period during which the vaccine had been marketed. None of the 99 was associated with Guillain-Barre syndrome at the end of the day. So, we resisted saying that the vaccine was protective. But we could say that the upper confidence limit on the potential risk of the vaccine was quite low.
So, that was in its way a success. What was not a success was the fact that from the day the manufacturer asked us and others to participate in doing this post-marketing study until the time we had a result that could go back to the FDA, four years elapsed. And the cost of the study was over $7 million. At the end of that there was nothing left. There was actually an FDA reviewer who asked about a related outcome, not Guillain-Barre syndrome, and our response was we would have to go construct an entire new data set in

order to do that. So, that was clearly an impossible thing to do.
So, this is by way of saying we need something that's a durable resource that can be used to answer a variety of questions, not all of which come from FDA. This is a slide that Jeff showed this morning. I just want to point out that the five organizations that participated in that study are really the backbone of Sentinel and all of the current PRISM organizations are part of that. So, that's by way of making the case.
The other piece of what I want to say by introduction is when we say how can PRISM be used, think really about what we're talking about when we say PRISM. We're talking about a set of four highly capable data partners that are in position of quality checked curated data in a standard format. And they all participate as volunteers in these activities.
A set of tools, all of which are in the public domain. But they are under rapid development so today's tool may take a while to make it onto the Sentinel website. But they are all intended to be in the public domain, partly with the hope that others will enhance them.
And thirdly, there is a set of coordination capabilities.
So, when we say, as a frame for this conversation, how can PRISM resources be used? Well, high level there are three ways. One is anyone who is interested in working with any of the data partners can just do that. And frankly, our advice is if the study you're interested in, as the initiator of the study, is one that can be accommodated by a single data partner then work with the data partner. It's always simpler to do that.
So, Kevin Haynes is here from HealthCorps. He's one of the data partners. If this is a study you can do with HealthCorps, do it with HealthCorps. If you can do it with Humana, then do it with Humana. The big advantage of PRSIM is if there is a study that really needs more than a single organization, can it be done in a coordinated way? And this has always been FDA's intention. From before Sentinel has stood up and was able to do the least little thing as Mini- Sentinel, FDA made a commitment to say it intended to build a national resource that would be accessible to a much larger group of users.
And that commitment has been there all along but has gained salience as FDA has taken a leadership position in articulating the case for a national system for evidence generation. And it sees the Sentinel resources as being a major component of that.
One way to take advantage of the coordination capabilities is through the Reagan-Udall Foundation's IMEDS program, which is even now reaching out to industry. In particular, the purpose of IMEDS is to create a more convenient way for industry to engage with PRISM data partners and Sentinel data partners more generally. That is scheduled to really take wing and become operational during this next year.
IMEDS, for the time being, is focusing on using the modular programs that were discussed by Jeff earlier and others have mentioned. For more sophisticated programs, IMEDS isn't currently entertaining those, though it does intend to do that.
And there is still sort of an ad hoc system for doing that. For instance, James Stark is going to talk about the work that Pfizer is doing with a team that reports to Jeff -- is not part of the Sentinel team -- that is helping to coordinate a study involving a number of the data

partners.
So, we currently do have capabilities, they're getting better, and we're going to hear form James about the study that Pfizer is sponsoring as a worked example that we can then use as a point of departure for a panel discussion.
So, James, thanks.

DR. STARK: Thank you, Rich, for the introduction. Thank you for inviting me to speak here. As Rich said, my name is James Stark and I'm an epidemiologist at Pfizer. I'm going to share with you Pfizer's experience of working with PRISM to conduct and observational safety study in support of TRUMENBA's post-marketing commitment to the FDA. This is my disclosure.
So, briefly I'm going to provide a background of the vaccine. I'm going to spend the majority of the time discussing the motivation and the process of how we engage PRISM. I'm going to comment on the status of the project. Then I'll also conclude with a comment on the future of the study. Throughout I'm going to try to emphasize what has gone well and the areas that can need improvement.
So, TRUMENBA is indicated for the active immunization to prevent invasive disease caused by Neisseria meningitides Group B, for use in individuals 10-25 years of age. The CDC recommends that a meningitis vaccine may be given to individuals 16-23 years of age. The vaccine was approved for use in October 2014. It can be administered in a two-dose or a three-dose schedule.
According to the U.S. prescribing label, TRUMENBA should be used during pregnancy only if clearly needed. Similar to other clinical trials, TRUMENBA -- pregnant women were excluded from the TRUMENBA clinical trials and there have been no adequate well-controlled studies conducted in pregnant women to date. Pfizer actively proposed and committed to a post-marketing study evaluating the effect of TRUMENBA in a population of pregnant women.
In 2014, we evaluated the options to conduct the study. Those options include a traditional pregnancy registry or a database study. Pfizer had successful experience conducting a pregnancy study using multiple secondary data sources. In the EU, this was specifically the Varenicline Pregnancy Cohort Study, using Swedish and Danish national registries. That was a commitment to the FDA.
In the U.S., we had recent advances in using multiple databases for the evaluation of vaccine and drug use during pregnancy. Research led by Dr. Allison Naleway using the vaccine safety data link, and Dr. Susan Andrade using MEPREP, has advanced pregnancy identification algorithms in these data sources for this purpose.
Furthermore, two protocols proposing similar algorithms using PRISM data authored by Dr. Alison Kawai posted on the Mini-Sentinel website in 2013, suggested the opportunities to use the VSD and Mini-Sentinel in the U.S. are available, enabling the access to multiple data sources at once to cover a large exposed population. This could achieve similar

objectives as a registry, but with potentially far greater methologic rigor.
Pfizer is interested in exploring approaches that address well-established limitations in pregnancy registries. In addition, the FDA's public meeting that Dr. Gruber referenced, titled Study Approaches and Methods to Evaluate the Safety and Drugs of Biological Products During a Pregnancy in a First Approval Setting was held in May 2014. This reassured Pfizer's decision to propose a database study for a post-marketing commitment.
So, we spoke with investigators at Kaiser and decided to pursue a study using the data from the vaccine safety data link. Dr. Allison Naleway from Kaiser Permanente Northwest worked with us to draft a study protocol and request access to the VSD data partners.
For those of your not aware, a previously developed algorithm was revised to run in the VSD data, which identifies pregnancies and the timing of pregnancies using ICD-9 diagnosis and CPT procedure codes. For this study, outcomes would be reviewed in the electronic medical record. The mothers are linked to birth certificates, death certificates, and state immunization registries.
A protocol was authored and submitted to the FDA in early 2015. Shortly thereafter the FDA endorsed the proposed study with some minor comments on the protocol. Nearly all VSD data partners reviewed the protocol submitted to the FDA, and agreed to participate.
TRUMENBA was approved in October 2014. The protocol was submitted to the FDA in early 2015. In January of 2015, the FDA approved another meningococcal B vaccine, Bexsero, for marketing in the U.S. The first set of ACIP recommendations occurred in June 2015, which resulted in a category B recommendation for young adults, aged 16-23. This means that doctors will make decisions on an individual basis and is not in the list of routine vaccinations.
Subsequently, the label for TRUMENBA was modified in April of 2016, allowing for a two-dose schedule instead of three. In the summer of 2015, we learned that several healthcare organizations in the VSD chose Bexsero for their formulary. As a result, the study population available for this study decreased significantly.
So, the question at hand was how do we proceed with our proposed database study with limited potential exposed pregnancies using the VSD data sources? We were dealing with a limited exposed population with moderately rare outcomes, which was the crux of the problem. So, we were confident in our design, choice of collaborators from the VSD, and the formal FDA comments were minimal.
So, based on internal assessment, we remain committed to this type of study approach. But we would need additional data sources that can increase the number of exposed outcomes. And we need these data sources to be able to have a capability to identify the timing of when the pregnancy occurred, the pregnancy outcome itself, information of the timing of exposure, the vaccination, and we would potentially need access to the medical records.
So, after conferring with Dr. Naleway, we thought the PRISM data sources might be applicable. At this point in time, this was December of 2015, the PRISM pregnancy

protocols which were demonstrating proof of principle were well underway. We thought we could get some early feedback on the capabilities that might be available to us.
So, we reached out to Harvard Pilgrim Healthcare Institute to gauge their interest and to learn about the status of the proof of principle studies. We convened a series of meetings with Dr. Naleway, Jeff Brown and Susan Andrade. We included Susan because she has a wealth of experience in this area and is a consultant on the PRISM studies.
During these meetings, we developed a process for data access, clarified roles and responsibilities, and we prepared a scope of work. By the second quarter of 2016, this year, the contract was in place for the first phase of this study. Harvard Pilgrim Healthcare Institute serves as the coordinating center, and they are responsible for the contract, querying the data partners, and managing the study.
In addition to the Harvard team, both Allison and Susan remain on as consulting epidemiologists, given their expertise in the field and their use of databases for pregnancy studies. In pursuing this relationship with Harvard, it was very clear that they were well connected with the Sentinel PRISM users and they had a lot of knowledge, obviously, of Sentinel PRISM. We felt like this team collectively was going to be very useful and helpful and very good, essentially, for our study. Second, they were very flexible in developing a contract and allowing us to include other epidemiologists to support this effort.
The study is divided into two phases. The first phase focuses on understanding the data from each of the partners, which means using the Sentinel tools to query each data partner for exposure counts, to understand the uptake in our study population, among other important data points. By doing so, we can now identify potential data partners for the full study which is essentially phase 2.
To Jeff's credit, he devised this two-phase process to enable flexibility in understanding which data partners will participate based on the queries. In that sense, it's a feasibility assessment. And I recommend others in doing these types of PRISM-based studies to approach it this way, where you basically get to know your data partners and the Sentinel system before you commit to something larger with more resources.
So, Harvard sent a letter of interest and held multiple teleconferences with the data partners that comprised Sentinel. Through this process, they identified eight partners who have expressed interest, and eight partners who have declined, and one partner who remains non-committed at this time.
A critique I have of working with Sentinel PRISM thus far is the voluntary nature of data partner participation. With limited understanding in advance of which partners would want to participate in a particular study and which would not, independent of exposure availability.
For some partners the decision was very clear. TRUMENBA was not included in the formulary, and therefore, we couldn't collect data. But for other partners the decision was not as clear. I give a lot of credit to the project team as they have been trying to work with

the partners to understand why they may not participate. But I think it will be useful for accessing PRISM in the future if there was some guidance made before engaging that could be available to people, to sort of get a sense of why a partner would participate and why they would not.

So, finally, I'd like to touch on some of the positives and challenges from this process thus far. Earlier I commented on the value of working within the system, such as access to the experts, flexibility, and the contract design approach to enable a feasibility assessment with a data partner as prior to committing to a full study.

Areas that pose a challenge included making the initial contact with Harvard Sentinel. It took some time to reach the appropriate people at Harvard. So, I think a process for how to do that moving forward would be useful. Second, as mentioned, having more clarity on decisions as to data partner participation before going into this process would be useful. I don't think it would have discouraged us, we still would have pursued this, but I think it just would have been useful to understand the boundaries of the data partners. Essentially, just because they are a data partner does not mean they will participate and I think that should be clarified.

Finally, the availability of recent and fresh data varies by each data partner. It made it a little bit harder to understand how many counts of exposed population we had. Data partners refresh their sense of data at different time points. Some counts that we have are up to date, we use fresh data. I think technically outside the Sentinel system so it was very fresh. Other data partners that we had were six months older or even a year older. So, I think it would be useful to understand the refresh process more clearly.

So, the in the next steps we'll focus on finalizing the study documents and preparing for the full study. Thank you. That concludes my presentation.

(Applause)

DR. PLATT: Thank you, James. So, we have five minutes for questions about James' presentation and his experience, and then we'll move on to the panel discussion. While waiting for hands to go up, I'll say this issue about who participates among the data partners is data partners decide. All of Sentinel -- one of the foundational aspects of Sentinel is that every data partner participates voluntarily, retains control over its own data and can use it for what it wants to. And even for the PRISM activities, every activity is opt-in for the data partners. So, I realize that creates a certain amount of uncertainty, but we've been extremely careful to be clear that the data partners voluntarily sit at the table. Sentinel and PRISM don't sort of provide access. This is an engagement of equals, but data partners are more equal than we are in this regard. So, more clarity about that I think makes a lot of sense.

One of the things about IMEDS is that the data partners are committing in advance to participate in IMEDS. They still have the right not to participate in any particular query, but IMEDS is finalizing contracts with them to participate in responding to a certain

number of queries each year. So, that's a little better clarity than, well, if you knock will anybody be there.
Walter?

DR. STRAUS: James, thanks for your presentation. I wonder if you could just talk a little bit about the level of involvement of the sponsor and the design and prospective conduct of the study. Obviously, you nicely described the particular challenge that Pfizer faced, but I'm wondering what the role has been of the sponsor in helping work with the research partners to design the study, as opposed to present the problem to the research partners and then have them really take it from there.

DR. STARK: So, I guess two points. First, Kaiser and I had drafted a protocol based on their -- you know, the EHRs. And we submitted to the FDA and we received minor comments. So, we had something in place. When we took that protocol to the coordinating center, PRISM, they were receptive to the protocol. I've been working very closely with them to modify the protocol so that it's now on the claim. We had to sort of transfer from this sort of EHR/EMR type of design that's something more focused on claims, and that's changed some of the ways we've analyzed the data and how we're collecting the data. So, I've been relying more on them to handle that aspect.
But in terms of the partnership, it's been very well, very good. They've sought my input on how I would approach it, I've asked them multiple questions. But I would say that this is a really fantastic team that we've put together and Jeff has at Sentinel Harvard.

DR. PLATT: Others? We've got a minute. Okay, I will fill that minute then, unless somebody
raises their hand, by making two more points. One is about how does the data partner decide whether to participate in the study. On the one hand, I'm a little hesitant to speak for the data partners. But one important issue is bandwidth. One of the advantages of PRISM is that at the beginning of each year we negotiate a level of activity which FDA then decides how to use. The data partners can staff for that level of activity. That's what IMEDS is trying to do as well, saying, can you staff for this level of activity.
So, when a protocol-based study opportunity walks through the door, particularly one that may take a fair amount of commitment, the question is do you have bandwidth to do that right now or can you staff up in time for it? And the answer to that is maybe we have to see. So, I think that's an important piece.
Now that the light is blinking, I'll answer a question that wasn't asked, which is how can it be that the same organization that coordinates for FDA can coordinate for industry? And there is a good conflict of interest policy at Sentinel that basically creates a firewall. So, if you look back at the structure that James put up, the epidemiologist at the Sentinel operation center who is leading this is Cathy Panozzo, who is in the back row. She doesn't

participate in Sentinel activities dealing with product issues. The same for the statisticians. So, there is good separation there.

Okay. We've moved to the panel section of the session. So, let me ask our three panelists to join us. Our panelists are Dan Salmon, who is an associate professor in the division of Global Disease, Epidemiology and Control at Johns Hopkins. But the real reason I'm delighted that he's part of this panel is that Dan was the guy who got this all started. When the H1N1 need arose, it was Dan who was in the hot seat for the government. And really Dan had 26 hour days for quite a long time then, sort of pulling this together. Dan is also the guy who decided to name this enterprise PRISM. So, we owe Dan a lot.

Fran Cunningham is the program manager for Pharmacoepidemiology and Outcomes Assessment at the Veterans Administration.

Harry Seifert, we've already heard from at JSK. I'll introduced Steve Anderson as my boss at FDA.

Steve said he's not going to make prepared remarks, but you better not just be silent here, Steve, for this session. At least my cheat sheet says Steve is not going to give additional remarks, but that will be unacceptable. (Laughter)

The promise we make is this session will end at 4:45 no matter what. We didn't talk about a preferred order, so if one of the three of you wants to go first in your remarks you should say so, otherwise I'll ask Dan to kick us off. Is that okay?

DR. SALMON: Thank you, Rich. It's really a pleasure to be here today. Thank you for the invitation. It's amazing to see how far PRISM has grown and how much is being done. So, it's an honor to have a chance to see this and to share my thoughts.

You asked me to kind of tell the story of what was the impetus or the desire to initially develop PRISM and my thoughts on where it might go. So, I'll try to limit my thoughts to that.

For us, with H1N1 in 2009, it was all about size and clearly size mattered for active surveillance. We were looking at the VSD and while it's quite large, this was a vaccine that was going to be rolled out with inadequate supply at first, and uncertainty as to where the vaccine would be delivered. So, while eventually enough people in the VSD might get the vaccine to do a study, this would take a lot of time. Plus, a lot of those people would get vaccinated outside of their normal medical home. My kids were vaccinated at school. So, if they had been, say, covered by Kaiser, Kaiser never would have known.

So, it was really the desire to put something together quickly that could answer safety questions that arose as fast as possible. What is quick from a science perspective is very, very, very slow from a political policy and news media perspective. So, time is clearly quite relative.

It was remarkable that all these pieces had been put together and were kind of waiting for such a crisis to arise. And largely the work of Rich and others have allowed it to come together as it did. So, that was really the impetus. To get something together that was

large, that could answer questions both for prespecified outcomes but also if something we didn't anticipate arose that we would be likely to be able to get an answer to that question, and would capture vaccines delivered outside of the medical home. So, that was the impetus. And it's amazing what other potentials are there.

In terms of other applications, I guess let me share a couple of perspectives. The first is, as an academic, there is amazing potential here to do studies. I think that people in academia are just becoming aware of these sorts of large databases although they've been around for decades. It's amazing from the safety perspective and effectiveness perspective, but all across public health and medicine how much could be studied and would benefit from this sort of infrastructure.

So, I think putting thought into that would be really helpful. I think part of it might be that of advertising and getting the word out that in fact there is capacity here to study other things.

But there are also things that are important from an academic's perspective, right? My approach would be to find extramural funding. Maybe I want to go for an RO1 or maybe I want to find some other funding source. So, all sorts of issues arise. How do I look at what the capacity is in PRISM and match it to what my study objectives or hypotheses are? How do I put together a budget? How do I know that the partners are going to be on board in order for me to submit a proposal? There are all sorts of issues that I think would make it more appetizing to academics.

And I think this is an important piece for moving forward. Having spent time both within government and in academia, it's great that PRISM Sentinel can meet the needs, one would hope, of FDA as, presumably, VSD meets the needs of CDC. And these are two really important agencies that do great work in public health. So, if their needs are being met that's wonderful.

But there are other needs out there, too. And I think there are other qualities that can really be brought to bear. In my opinion, having watched what's happened with VSD over the years and just a little bit about PRISM, I think taking advantage of the intellectual and scientific expertise outside of government is incredibly important. And, in general, academics don't want to be just data managers, they want to help decide what gets studied and how it gets studied. They want to do the analysis, and they want to interpret the results.

And there needs to be opportunity for junior faculty to develop into senior faculty. And having that involvement usually leads to more innovative work and higher quality studies, and sometimes even a more fair and scientifically accurate interpretation of the data. So, I think involving academics and others outside of government is really important.

And I'll put a second hat on because I'm also a member of the public. So, I'm going to try to speak to the public because we're all here in public health, but sometimes we don't hear from the public so much. I get that this is somewhat of a controversial topic, but in my opinion, we need to meet the needs of the agencies, but we also have to meet the needs of

the public. There are safety questions that have been out there for a long time that aren't being studied or are barely being studied.
And the NVAC has put a lot of work into thinking about how one prioritizes vaccine safety. And there are many factors. NVAC argues, and I would concur, that public interest is one of them. And, I think in particular, for what gets studied. Not so much how to study it or how to interpret results because they don't have the expertise, but for what's important, I think we really need to listen to the public.
Thank you.

DR. PLATT: Thank you. Fran?

DR. CUNNINGHAM: Thanks for inviting me. My name is Fran Cunningham. I was asked to speak today on behalf of a healthcare system's point of view, specifically VA healthcare system. As you may know, VA serves as a healthcare system but we also conduct surveillance as well as research. So, as I'm addressing how VA could use PRISM or the advantage of PRISM to the healthcare system, I'll try to wear all three hats, so to speak.
From a healthcare system, as you may know, or for some of your that may not, VA takes care of a very small patient population, approximately 6 million patients, about 4.9 million use that system consistently or continuously. What's unique about our patients is first and foremost they are very selfless. They gave themselves to us as a country. So, they are very special to us. For us who work in VA we worry about them and we really care about them. We want to make sure that we take every possible angle we can to take care of them. That's why our center for safety exists. We have a lot of good researchers and collaborators in VA that we work with.
To that end, our patient population tends to be a bit older. They have chronic disease states. If you think of the VA as a whole, greater than 50 percent of our patients suffer from a chronic disease state at a moderate or severe level. So, it makes our patient population a bit different than any other group of patients when we begin to look at safety of agents, and more importantly, effusiveness of vaccinations.
When I talk about the chronic disease states, about percent of our patients have hypertension. Over 30 percent
have diabetes. 20 percent have chronic obstructive pulmonary disease. And a very large percentage of those patients have these disease states overlapping. So, if one looks at developing influenza, or getting pneumonia, respiratory failure is pretty significant in this patient population should those vaccinations not be effective. Effectiveness becomes very important for us in as much as safety. So, that's something to remember.
Secondly, with the most recent conflicts, we've increased the number of women in our system, specifically women of childbearing age. So, that's a group that we weren't necessarily used to taking care of. It's also a group when we're looking at safety as well as

effectiveness of vaccinations we need to look at more closely. When we look at pregnancy, a lot of our young women may become pregnant, but of course they leave the system after they deliver their child and then come back. So, we don't necessarily see what happens to the infant at that point in time.

So, that's us from a healthcare system. From a surveillance system for many years we've looked at medication safety. More recently we've looked at vaccine safety. I have to thank Dan, of course, and Hector Izurieta. If it were not for those two I would say that our vaccine safety system, as small as it is, wouldn't have been built because we wouldn't have the impetus to push our system to have a vaccine registry, so to speak, or an immune database. So, we do have that now and we're able to address vaccine safety, specifically influenza and Zoster at this point in time with the hopes of moving forward to pneumonia and Tdap.

So, we also do research and we have the capability at several different levels to conduct research. When we look at PRISM and what the advantages would be, I'd say it's probably three-fold. From being in a position last week when I was in a meeting and someone asked me, when you're at the safety of influenza vaccine, what's the effectiveness of the quadrivalent vaccine? I don't know. Are you looking at it? No, we're not. We're looking at the safety at this point in time. So, I thought I was kind of out of the woods and then I get an email, why aren't you looking at the effectiveness of the quadrivalent vaccine? So, I could see right now PRISM being a group we could go to and say, are you looking at this? How are you looking at it? In what patient population are you looking? Can you stratify for patients with comorbid conditions? Can you make a patient population look more like ours? Our patients, when they come in to the system, they stay and they stay. They do not leave until death. They do use other healthcare systems, most frequently Medicare, but when we have our patients in our system we keep them for life. So, that's an advantage. Effectiveness being one of the areas that we could look at.

Another thing that I recently learned of and saw an example of today was the signal detection system, which I think will be very good to look at. Not necessarily or only for new vaccines, but old vaccines in special populations. Or in patients that have multiple comorbidities that we're used to looking at. And looking at if there are certain safety signals or safety issues that we should be more worried about in those patients. The signal detection would be something that a healthcare system, especially a healthcare system like ours, would be interested in using or seeing used.

I guess, lastly, which I mentioned earlier, it would be looking at women, especially women of childbearing ages and being able to get more information for the effectiveness of vaccine in that patient population.

So, from my standpoint, I think the utility of PRISM is, one, an excellent program, has developed relatively quickly. And I can see benefits from a healthcare system that even has a good database and has lots of work that's been done that we could even use it and see more being done over the years, especially as newer vaccines come out. Vaccines for

older patients and the sicker patient population.

DR. PLATT: Thank you, Fran. Harry?

DR. SEIFERT: Hi, my remarks are not prepared so nothing I say necessarily represents anything that anyone at GSK thinks. I'm completely on my own. I think that will make the lawyers happy.

Actually, while Dan was speaking I actually had some quasi-prepared remarks but I tossed them out because I think a lot of the issues that I was concerned about I raised previously. But I think there are sort of three issues that I'd like to bring up, or three topics I'd like to very briefly address here.

The first relates that many of the questions that you raised about access and rules of engagement and guidance about how to use it in funding I also would apply to industry. But that also, I think, sort of reminds me of the second point, which is one of communication. I applaud the Agency for having meetings like this. I think to a large extent the Agency has been fairly transparent about PRISM and its strengths and limitations. But I think the operational aspects about how do we engage it could perhaps be better publicized. I think the relatively recent placement of the protocols and essentialized database webpage that we can all access I think is great. But I think getting the information out there to academics and industry would be a big help and could increase utilization and understanding of the database.

I think, of course, the next question or the next piece of the communication is not specific to the sponsoring agency or to PRISM necessarily, but how do we communicate the results, not just to ourselves but also to the patients? Also, how do we understand? So, it's the inward listening part of communication. It sounds very new age-y but how do we understand what the patients' concerns really are?

Is it whatever we're getting sued over next? Or are there recurrent themes of patient concerns or barriers to vaccine uptake and utilization? I remember you doing work on that several years ago. So, I think that that communication piece, the two-way communication piece is important and could increase the use in value of the system.

Finally, the last piece, and it's something you touched on, is safety, safety, safety. Safety and risk of harm are important, but without the context of benefit or effectiveness I'm not sure how to interpret that. I mean, from a clinical standpoint as a former anesthesiologist, I'm graded with telling patients about all the terrible things that my drugs and interventions can do, but we also have to remind them that there is really some good that can come of this. Very few patients opt for major surgery without anesthesia.

Similarly, the patients are being referred for vaccinations for a reason. I think we have to be able to demonstrate that scientifically and communicate that.

Thank you.

DR. PLATT: Thanks. Those were great comments. I really appreciate your --

DR. SEIFERT: I may be asking you for a job if word gets back home -- (Laughter)

DR. PLATT: So, we're in the summing up phase, the discussion period now. So, although Steve isn't making comments as part of the panel, it would be great if you were willing to sort of start off the discussion part of this session?

DR. ANDERSON: Well, I think we should just go to questions.

DR. PLATT: Questions? Comments? Let me start with Bob and we'll work our way down.

DR. DAVIS: So, Fran, I was delighted to hear of the potential interest to engage in this kind of project. Do you think that the Department of Veterans Affairs would be interested and, I guess, open to making the data available for these sorts of routine queries to do pharmacovigilance? Because it's kind of a different kettle of fish than what the VA has typically done in the past. It's a very flexible, fluid system, of course, but I'm just curious as to how you think that would proceed?

DR. CUNNINGHAM: I don't know about opening up the data. I know that there are a lot of investigators that are housed in VA that collaborate with others. So, that's always the capability, especially across the entire VA system. So, that's typically how VA has worked with other universities or with other entities, is they work with a single investigator and then work collaboratively.

DR. PLATT: Walter?

DR. STRAUS: I wanted to just build on a point that Harry made around communication. One of the phenomena of our time is that there is -- well, firstly, there has always been skepticism around vaccines by different groups for different reasons. Groups that question the merits of vaccines. What's really changed in the last few years is the ability through blogs and through the internet to disseminate information that may not be accurate. I think given that, there really is an increasing demand to assure that there is effective communication of benefits and risks of vaccines. What I would just encourage and throw out is that as the Sentinel program and PRISM grows that there be increasing focus on effective communication in support of the excellent surveillance activities and other activities that are undertaken by Sentinel.

DR. PLATT: Great. Additional questions? I was going to call on you anyway, Kevin,

so I'm glad you raised your hand.

DR. HAYNES: I actually wanted to follow up with that. Kevin Haynes with HealthCorps, one of the partners willing to open up bandwidth to industry or academia as I have time.

But I wonder about the data partners being a conduit for that communication as well. Obviously, given our role, we're not just a payer. We're really also interested in the health of the patient, keeping them out of the hospital as well, right? So, I think there is a lot of benefit to engaging the payer. And I know that Sentinel has done that with safety concerns. And PCORnet also adds to some of that dissemination.

One point that I wanted to add to Dan, listening to you, when you said that academics don't want to just be data managers and whatnot. Data partners don't want to be either. We have a fully functional staff of epidemiologists, biostatisticians and whatnot. We have found great pleasure in working with Sentinel, PRISM, and all of the DRN, NIH, PCORnet, everything in engaging in the science aspect as well as understanding the benefit design pieces of, well, that's why I don't see anybody on that drug because they have this type of benefit design. And that's a strength of the relationship with the data partners. So, no, we're more than welcome to hear what types of questions would be of interest. Really, just from the data partner perspective, we're here to help.

DR. PLATT: The reason I was going to call on Kevin was because I thought it was important for everyone to hear just how high quality the science is that data partners bring to the table, and how critical we think that is to the success of PRISM.

Among the things we say are most important, one of the foundational issues, is that the data has to be fit for purpose. And nobody understands that fitness for purpose better than the people who created that data and live with it all the time. So, they bring deep system knowledge as well as the sort of scientific credentials to make that work. We think that's an important piece of Sentinel as a distributed system that incurs a fair amount of overhead compared to one large data set.

Several people have heard me say during the various breaks how much I enjoyed today because it sort of throws into sharp relief how deep the scientific bench is at the manufacturers, and it's good to give appropriate recognition to the data partners who also bring deep scientific expertise.

Any other questions or comments? Panelists, anything you want to say to one another or anyone else?

DR. ANDERSON: So, I think it is important that FDA's bigger vision is to increase access to this. So, I guess what I would put to the panel is what do you think the barriers to access are? I think to people in the audience as well, especially academics. I know industry, but I think there are a lot of stakeholders here that probably want access or may be sitting in your chairs thinking about it. But what do you think the barriers to access really

are?

DR. SALMON: I'll take a shot at that. I'm sure there are many. To me, one big one is money. If I look at having health prioritized vaccine safety research within the federal government, the problem was we were only funding the top few. There really is a tremendously more -- not that vaccines aren't safe, vaccines are very safe, but there are many unanswered questions.

In 2009, I wished I knew why the 76 vaccine caused Guillain-Barre syndrome, what that biological mechanism was, because it would have been really helpful. That's obviously not a question for PRISM, but there is a lot that can be studied. I think funding is a major issue. It just is.

Especially if one wants to fund a diversity of priorities. Because presumably FDA will prioritize what FDA's priorities are, as CDC will do, and other industries will do. But that may leave many topics that are important to some that don't have the pocketbook that really need to get studied.

Then, I think, related to that is bandwidth, which we heard described from the data partners. And money can probably solve a lot of that. You know, people can be hired and so forth. But there are still going to be limits there. So, that's my immediate response.

DR. PLATT: Harry is going to weigh in, but I'll just say that the FDA is very sensitive to the fact that PRISM is an expensive proposition. It's usually out of the league of investigators who have NIH support.

So, compared to a $7.something million Menactra study, the thing goes away, PRISM is a great deal. Compared to actually having to write a check, it's still expensive. And it may become less expensive, but it's unlikely to become cheap anytime soon.

Harry, you may have the last comment here.

DR. SEIFERT: Well, I think a roadmap for how to engage PRISM by outside organizations or individuals would be healthy. Whom to contact, what are the expectations, what are the capabilities. Even if it's in relatively high level terms, what are the rules of engagement and what can be expected, I think, would be very helpful. I think James alluded to some of that in terms of knowing whom to contact even in the beginning. So, aside from the obvious things like money, I think a roadmap would be helpful.

DR. PLATT: So, maybe a recommendation to put information like that on the Sentinel website would be worthwhile.

So, I think we can declare victory for this session. Thank you to the panelists and thanks to all of you. Steve is going to take us home.

(Applause)

Closing Remarks:

DR. ANDERSON: I think just given the lateness of the hour, I have 15 minutes and I'm not going to take 15 minutes. People probably want to get out of here after being here the whole day.

I'm going to start with thank yous because I don't want to end up missing people. First of all, I wanted to thank all the speakers, the panelists, the presenters. I thought this was a great workshop. All of the sessions I thought were very valuable. I just wanted to sort of thank everybody for participating.

I also wanted to thank the audience members, the people that travelled here. Again, I think you played an important part with your questions as well.

As far as within the Agency and those people that helped with organizing, I wanted to thank my OBE staff, the Office of Vaccines was really helpful as well. I wanted to thank OCOD because OCOD does the yeoman's work of trying to help us organize the registration and organization of the room. So, I wanted to thank them.

Thanks to the Harvard Pilgrim staff, to Rich Platt and his staff. There are a number of you here, probably 10 people that came down from Harvard. So, I wanted to thank you for taking the time out of your busy schedules as well. We appreciate that.

I wanted to thank the data partners, too, because we couldn't do this without the data partners. I think you play sort of what seems like a very background role seemingly, but we all recognize how important it really is. So, thank you guys for all the work that you do. It's a beyond thankless job, but we do appreciate it.

I especially wanted to thank Azadeh Shoaibi again and her crew, Kinnera Chada and Joyce Obidi, for all the work that they've done in organizing this.

Just as far as closing notes, information for the transcripts. The transcripts should become available, I assume, within anywhere between three to six weeks on the website. The slides we've got to get permission in order to do that so we'll be working on that as well. Anything else I forgot as far as what's going to be posted.

And then as far as issues and questions that came up, I just wanted to do some quick summaries because I didn't want you to think I wasn't listening. I was madly writing down -- I ran out of pieces of paper. I have several different pieces of paper with comments.

A question came up about what if an alert is generated in TreeScan how would it be resolved. I can tell you, Rich, our group, have sort of sweated this out. What I do want to say as far as TreeScan is, you can see it's not massively deployed right now or we'd be doing every vaccine. There is a reason for that. Because we recognize some of the challenges with implementing it. So, we're sort of taking our time and rolling it out very slowly. We recognize there are issues with if there is an alert, what do we do. We'll set up protocols and procedures and have those in place to deal with that. We want to deal with those alerts as quickly as possible.

I'm going to say, the TVER tools, the PEPR tools are a great start. I think we all realize

we've got to do a bit more as far as validating a potential signal if it pops up.
There was a question raised on data lags by Frank, Harry, Karen, and Bob, and everybody on my panel. So, what are we doing about that? We did a contract for a project this past year to actually tackle that issue. So, we are tackling the issue of the data lags. We're hoping to use it, I think, depending on what the final example is, whether it's influenza or another vaccine. We're planning on working a bit more on that. Our goal with that project is to have responsiveness anywhere from -- I think right now our limit is two weeks as our lower beltline. I think we realized in the end we've got to go down further.
Then, yes, I think we did adopt Bob Davis' perspective, which was we'll probably start with one or two or three data partners, keep it small, and then perhaps think about whether it should be expanded out. So, we do have an answer for that question.
We take the point also that VSD and PRISM are complementary. I think we have a lot of discussions to have with our VSD colleagues, with our CDC colleagues, on how that complementarity will work out. That has to be done between the agencies, but those discussions will get underway as well.
A question about access to the system and cost. We just had those discussions. I'll take the point back about we need a better way to communicate how people can get access. That might be on the website and putting postings on IMEDS' website as well as the Reagan-Udall as well as the Sentinel website.
There was a question about how priorities in PRISM are defined, how are projects determined. Right now, that's an internal process. We have governance procedures that we're standing up. Just recognize that this is a relatively new enterprise to us.
Mini-Sentinel went on for three or four years and then we just put Sentinel up at the beginning of 2016. So, we are getting the pieces in place. It's going to take us time.
As far as how can industry and stakeholders have input, the plan is to have some process, some public process. We don't just want to give industry access but we want to give industry and the public access at the same time. So, that type of feedback might occur as part of our Advisory Committee process or other types of public meetings.
Those are the major items that I had on my list. Given the late hour, again, I want to thank everybody for attending, and enjoy safe travels back. Thank you, all. I appreciate it.
(Whereupon, at 4:52 p.m., the PROCEEDINGS were adjourned.)

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I, Carleton J. Anderson, III, notary public in and for the District of Columbia, do hereby certify that the forgoing PROCEEDING was duly recorded and thereafter reduced to print under my direction; that the witnesses were sworn to tell the truth under penalty of perjury; that said transcript is a true record of the testimony given by witnesses; that I am neither counsel for, related to, nor employed by any of the parties to the action in which this proceeding was called; and, furthermore, that I am not a relative or employee of any attorney or counsel employed by the parties hereto, nor financially or otherwise interested in the outcome of this action.

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My Commission Expires: March 31, 2017