FOOD AND DRUG ADMINISTRATION (FDA)

PUBLIC MEETING

STUDY APPROACHES & METHODS TO EVALUATE THE SAFETY OF DRUGS & BIOLOGICAL PRODUCTS DURING PREGNANCY IN THE POST-APPROVAL SETTING

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A G E N D A

DAY 2

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P R O C E E D I N G S

MS. MOYER: Good morning. Welcome to the Day 2 of the Public Meeting, Study Approaches and Methods to Evaluate the Safety of Drugs and Biological Products During Pregnancy in the Post-Approval Setting. My name is Vicki Moyer, and I serve as a Regulatory Project Manager for the Center for Drug Evaluation and Research, Office of New Drugs, in the Pediatric and Maternal Health staff.

Your attendance today and participation, in person and via webcast, are sincerely appreciated. Before we begin, I would like to share a few housekeeping details. Please silence your cell phones, BlackBerrys, and other devices. Please check in at the tables outside in the lobby, if you have not already done so and you're just attending for today.

The agendas and discussion questions are available. Open public speakers need to sign in at the speaker registration table. If you have not checked in at the meeting registration table,

please do so; otherwise, you may not be able to speak. Alternatively, you may submit your comments to the public docket.

The slide presentations for all of our presenters will be posted on the FDA Web page with the meeting announcement. Transcripts of the meeting will be available approximately 30 days after the meeting. You are encouraged to post comments to the docket, which is open until June 30th, 2014, with your feedback.

Restrooms are outside of the main conference room and in the back area of the lobby. We will have one 15-minute break at approximately 20 minutes after 10 today, and that's the only break, because we'll be adjourning at 1:15, so we have a very busy and packed morning. The kiosks in the lobby are open for refreshments during the break.

Before proceeding with the first speaker and some introductions of the panel, I'd like to remind panel members to please introduce yourself when you speak so that it's clear to the

transcriptionist as well as the participants via the webcast.

Before introducing Dr. Michael Nguyen, I will like to go through the panel again to please introduce yourself, and I'd like to start with the participants on the phone, if you could please introduce yourself.

DR. HONEIN: Hello, this is Peggy Honein. I'm with the Centers for Disease Control. I'm an epidemiologist and the Chief of the Birth Defects Branch.

DR. NALEWAY: Hi, this is Allison Naleway. I'm an epidemiologist with Kaiser Permanente in Portland, Oregon.

DR. CONLIN: And this is Dr. Ava Conlin with the DoD Birth and Infant Health Registry located at the Naval Health Research Center in San Diego, California.

MS. MOYER: And can we start with Dr. Adrian Dana, please?

DR. DANA: Good morning. This is Adrian Dana from the Clinical Safety and Risk Management

Group at Merck.

DR. CRAGAN: I'm Jan Cragan from the Birth Defects Branch at CDC.

DR. HANSEN: Good morning. I'm Craig Hansen from Kaiser Permanente, Georgia.

DR. HOLMES: Good morning. It's Lewis -- I'm Lewis Holmes from the North American AED Pregnancy Registry.

DR. ALBANO: Jessica Albano. I'm Senior Director of Epidemiology at INC Research.

DR. COSTER: Trinka Coster, Pharmacovigilance Center at the Office of the Surgeon General.

DR. ANDRADE: Susan Andrade at the Meyers Primary Care Institute.

DR. CHAMBERS: Tina Chambers, Pediatrics, University of California San Diego, OTIS, and the VAMPSS project.

DR. IYASU: Solomon Iyasu. I am the Director of the Office of Pharmacovigilance and Epidemiology in the Center for Drugs.

DR. YAO: Lynne Yao. I'm the Associate

Director of the Pediatric and Maternal Health Staff in the Office of New Drugs.

DR. STAFFA: Judy Staffa, Director, Division of Epidemiology in the Center for Drugs in FDA.

DR. NGUYEN: I'm Michael Nguyen. I am the Acting Director of the Division of Epidemiology in the Center for Biologics.

DR. SAHIN: I'm Leyla Sahin. I'm with the Pediatric and Maternal Health Staff in the Office of New Drugs in CDER.

DR. HERNANDEZ-DIAZ: Sonia Hernandez-Diaz, Associate Professor of Epidemiology at the Harvard School of Public Health.

DR. BERLINER: Elise Berliner, Agency for Healthcare Research and Quality.

DR. GREENE: I'm Michael Greene. I'm an obstetrician/gynecologist at Massachusetts General Hospital.

MS. JOHNSON: Diana Johnson from OTIS Pregnancy Studies and UCSD.

DR. MITCHELL: Allen Mitchell from the

Slone Epidemiology Unit at the Slone Epidemiology Center at Boston University and VAMPSS.

DR. TASSINARI: Good morning. I'm Melissa Tassinari. I'm at CDER, Office of New Drugs, Pediatric and Maternal Health Staff.

MS. MOYER: Thank you. And now I'd like to introduce Dr. Michael Nguyen, Acting Director at the Division of Epidemiology in the Center for Biologics Evaluation Research, who will provide opening remarks.

DR. NGUYEN: It's a pleasure to be here this morning. If you open the Washington Post this morning, you'll notice that we have a winner amongst our panelists who got her living room identified to -- for a complete makeover in the Washington Post. They provided free design advice and -- to make it welcoming and to make a really striking impact, and I think that's what we're -- similar to here -- how I feel today. You know, it's not my living room, but it's something near and dear to my heart, which is pregnancy exposure safety, and what I'm feeling like is I just won a

free makeover, you know, in our guidance document.

And so, you know, I just want to take a moment and just celebrate this, because it's nice to know that systems that we have in place work. We invited -- you know, we created a space, invested the time, and invited the nation's experts. We have people on study design, we have experienced leaders on the registry -- and leaders who actually operate registries, patients with deeply personal and professional experiences, and fellow experts from other agencies in the military, and they're all here to help us, and I think it's just an amazing effort to see it happening.

We also opened this up for public comment, and yesterday we had ten incredible, insightful, well- prepared comments, and I just want to thank you, for those folks who participated in the public comment period.

And in my experience here at the FDA, I think these workshops have a profound impact on us, and I really want to underscore that, because

you guys are spending -- taking time out of your days and out of your careers to come here and give us this advice and share your experiences, and I'll tell you from firsthand experience, this crystallizes our thinking and catalyzes and accelerates the process of reform.

And I can't emphasize that enough. We take all of your advice. We take it back. We pore over the transcript. We pore over your slides, and it has a deep, meaningful effect on us. And why? Because it joins the real-world experience in academia and industry. It brings us up to speed on the theory behind these designs and focuses our resolve on the bottom line, which is really to provide meaningful information to patients and providers to help them make informed decisions about risks in pregnancy. And, more importantly, you guys give us practical, meaningful advice and wisdom.

So I want to just launch off a comment that was made by Julia Beck yesterday, that, you know, don't start with something hard. Start with

something easy. And I'll divide these comments into our three main audiences, and, you know, first is the patients; the second is the healthcare providers; and the third is really FDA and industry.

And the clear message coming out of yesterday was that, you know, to make this work, we have to establish a direct relationship with the patients. And you didn't stop there. That's what's great is that you didn't stop there. You gave much more thoughtful, practical advice. You said focus on those thought leaders. Focus on those cheerleaders, those influencers, to really make this happen. Ensure frequent contact. This was a message coming out of Tina Chambers' talk. You know, don't enroll them and then come back when the baby's born. Really make multiple points of contact to really deepen that relationship.

And this is coming from the representative from ACOG, and that's enroll, and not only enroll, but enroll early. And that helps us with what Dr. Hernandez-Diaz talks about with

left truncation, and it also really helps us get better access to medical records.

And really think hard about the informed consent process. Don't just reduce it from nine pages to one page, but actually transform it, try to transcend it, and maybe think about alternatives, like going verbal. I think these are very, very important ideas.

This is another idea that came out of Tina, Dr. Chambers, is reduce the barriers to participation. Think about two tiers of levels of participation, because it's hard. The commitment to share information with strangers and with institutions is a leap of faith, and so we have to think about how much of a leap of faith that is and how we can bridge that gap.

Think about more flexible alternatives to the, quote, unquote, per-protocol design analyses, with full medical record confirmation. Is there -- can we do with just a little bit less information and still derive meaningful information?

Another comment from Julia Beck, amplify the awareness through partnerships that pair your awareness campaigns with others. And she talks about giving not monetary incentives, but pairing with others, like giving gifts that are meaningful to them; diaper bags and things like that. And, finally, give back to the patient. Share those results and return the gift of participation.

So also -- the other audience we had was healthcare providers, and here we say physicians are the most trusted source of information. That was the clear message. So how do we build that trust with physicians?

And, again, it's -- the message is make it easy. Make it easy for them to connect patients with our registries. Establish methods that count for the increasing time and cost containment pressures, the demands of routine obstetrical care that Dr. Greene talked about in quite detail. Use the advantage of the electronic medical records and the practice-based triggers that seem to be quite effective, while keeping in

mind that we can all get alert fatigue.

And do what we can to simplify the thinking for doctors about when to enroll and how to enroll. And so they gave us three great areas of advice for this. First is create disease-based registries. Not only do you reap numerous benefits from simply economies of scale, method standardization, and increased comparability of groups, but, really, the greatest effect on the physician is that it simplifies that question of who should I enroll, and how do -- and what phone number do I give them, and what website do I give them? When you can simplify and consolidate registries, I just -- it sounds as if that's the way to go.

And then we even had some more aspirational ideas, such as consolidating registries and even considering the possibility of a universal registry. I think that's more realistic in probably vaccines areas, where I come from, but, you know, we don't get anywhere by not thinking big.

And the last audience is FDA and industry, and this is where Janet Cragan gave some really solid advice, I think, and that is move from guidelines to standards. And that wasn't just a hard line she took. She actually said, "Move from guidelines to standards, but allow gradations."

And it makes me think about the LEED certifications of like silver, gold certifications. And what it allows us to do is set a high standard, but then realize that there are real-world constraints to running these registries and allows industry to adjust their own product in their personal situation to those goals and standards that we all want.

And then consider and acknowledge the challenges faced by global registries -- this is a comment from Dr. Dana -- and the different privacy laws before we start requesting and expecting global surveillance for pregnancy.

So I'll end there. I really look forward to the talks this afternoon. It's -- and

I really thank you for your public service today, and I think it's going to make a really deep impact for FDA. Thanks.

DR. STAFFA: Good morning. I'm Judy Staffa, and I have the pleasure of moderating this morning's session, but before we get to that, we had a speaker on the agenda for yesterday who had a mishap yesterday and wasn't able to join us, but I'm really happy that Dr. Sandy Kweder, who is the Deputy Director of the Office of New Drugs, is able to join us and is going to share some remarks with us to get us started today.

DR. KWEDER: Well, good morning, everyone, and thank you, Commander Nguyen, for those great remarks. I really appreciated hearing your perspective, and I think everything you said was absolutely right on target, right on target, and a great way to start the day.

I apologize for not being here yesterday. I had an interesting flat tire mishap. The good news was that it blew, I turned into a parking lot, got a handicapped spot right in front

of a bakery, and was able to wait it out -- wait out AAA with great coffee and pastry.

I want to congratulate you all on being here and taking the time and energy to come here, whether you came from Bethesda or whether you came from California. And I want you to think for a minute now about why you came, what got you to summon the energy to get on the plane or to get in your car or clear your work calendar to come here. What was that? And we'll come back to that.

But I do also want to point out how far this field has come, and I -- gosh, it makes me feel old, but I'm thinking back, and I see some faces who I think were at that meeting, over 20 years ago, that FDA held. It was the first time that FDA held a meeting to talk about the lack of information on outcomes of exposure in pregnancy, and it was a wide- ranging meeting. Ruth Merkatz was who was the Director of the Office of Women's Health at the time, and a firecracker -- put together a meeting that I would say was quite controversial. That FDA would actually say we

needed data on outcomes in pregnancy was somewhat heretical.

That was in 1991, and I remember because I was about, oh, 36 weeks pregnant at the time. Okay? And as I look back, I think about the fact that I was pregnant with a young woman who is now 23 years old and assigned to her first submission, and I think about what time has passed and really how patience has paid off. Patience has paid off.

And at that time, we were talking about the need for any data. I mean, any data. And today, we're talking about how to refine the type of data that we collect. So it's now generally accepted that collecting data is an important task that we, as a society, need to take on with vigor and rigor, and that rigor piece is what we're talking about today; isn't it?

Back then it was convincing people that collecting data was important. Then there was this -- people would get gripped in the gut if you talked about actually seeking data, because to seek the data was to acknowledge that pregnant

women took medicines and were exposed to drugs. There was a real psychological barrier to collecting data, on the part of the healthcare community, because you would then acknowledge that someone was prescribing medications to women who were pregnant.

I think we've really, really made some important leaps between then and today. We were also in the position to say, "But who would do this? No one would want to do it." But we had one company who acknowledged the reality that there were exposures and had the gumption and put the money into trying to do the right thing and do the best they could, and that was Burroughs Wellcome. Burroughs Wellcome had put together a registry for acyclovir. We still talk about that registry today. They were the first, and it was because people in a company did the right thing.

And that example is one that I think comes up in almost every conversation about pregnancy registries. Allen, do you agree? I mean, we always go back to that. Was it perfect?

No, but it launched the recognition that this could be done.

And I'm so happy to see all of you here today, some of you who I know were at that same meeting in 1991, and I'm thrilled that you're still here and that you've all collect -- that the collective wisdom of you with the newer faces who I don't recognize some of you are determined to do right by this, are determined to make a difference for that woman who's sitting in her doctor's office or sitting in front of her computer and has been exposed to a medication, or someone has proposed to prescribe her a medication while she's pregnant, because she's quite ill, and are doing your best to get those data in a way that we can rely on so someone -- her clinician will have something to say to her.

I remember -- and one of the things that we often fixate on in this -- and I'll just remind you of the need to be practical. We often fixate on understanding what the risk of a particular exposure is, and we -- as scientists, we get very,

you know, down in the weeds on what's the relative risk, what's the attributable risk, and how big is the risk?

And as we seek rigor, I want to also remind us that sometimes, just as important as what the risk is to the patient is what the risk is not. Don't forget, to the patient, it's what the risk is not. This is not isotretinoin, because that's what she's worried about. Okay? This is not X, Y, or Z. So understanding what the risk is and understanding some of the parameters around it, that -- we have to take that seriously. But remember that almost everything we do has some translation into clinical medicine.

And I would also challenge you as a group, when you're thinking about how to reach out to the patient, how to make registries better, how to make them more scientifically robust, to also not forget that how we translate the information from those really intensive data collection efforts into meaningful information for patients is equally as important and not to lose sight of

that.

So I think we're in an enviable place compared to -- we would have envied this 23 years ago. It's a great place to be. And I would ask you now to think about that and ask yourself again, "What got me here? Why did I come here today? Why? What motivated me to come here?"

Maybe it's a personal experience you had with a patient or a family member who was pregnant. We all know them, right, or we've been them. Maybe that was it. Maybe it's you have a burning scientific question. But recognize that they're all women who are really depending on you to help figure this out and be bold. Think outside of the usual way of doing business. That is how we will make progress. And press us. Press FDA. Press us, but help us. Okay?

And I think -- seeing who's around the table, I think I can count on that on both counts. But, again, congratulations, think about why you're here, and turn that energy, when you leave here, into doing something different when you go

back to wherever you came from. Do something different. Take something you learned here to help us all take the next step.

So thank you very much. I look forward to being here for a bit, and then working with the staff to help us all make a difference. Thanks.

DR. STAFFA: Thank you, Dr. Kweder and Dr. Nguyen. So Topic 3, the basis of this morning's discussion is we're going to be looking at some alternatives to traditional pregnancy registries. So the good news is we have some fantastic speakers who are going to be sharing some really interesting efforts and programs.

They're not going to be able to, obviously, go into a lot of detail about the efforts they're making, but we've asked them to come and just give us a brief idea of the kinds of methods and data that they have been looking at or using to look at drug exposures in pregnancy and outcomes and then frame a discussion that we can then have on how these systems and ideas and methods can best complement the traditional

pregnancy registry ideas.

So that's the good news. The tough news is we have seven speakers to fit into the next two hours, so I will be riding my broom and asking people to stick to their time. So I trust you'll understand why.

Our first speaker is Dr. Allen Mitchell, who will be talking about combined registry and case- control approaches. And I won't be counting Dr. Kweder's time against yours, so that's okay.

DR. MITCHELL: Thank you very much, and I very much appreciate the invitation to attend this session, and I'd even be willing to cede some of my time to what Sandy said because so much of it bears directly on the kinds of things that concern us.

I was asked to speak about the combined registry and case-control approach, or, as we call it, the Vaccines and Medications in Pregnancy Surveillance System, VAMPSS. So although I'm from the Slone Epidemiology Center at Boston University, you'll see the logo on the bottom

right is from the Academy of Allergy, Asthma, and Immunology, which is the sort of parent of the program, as you'll learn more.

One of the challenges that we were presented in this morning's session was to describe some of the limitations with pregnancy registries. And, obviously, in preparing the slides, I couldn't anticipate yesterday's discussion fully, although I think some of it was reasonably predictable.

And so I'm going to begin -- I hope. Let's see. Yeah, with this disclosure, which is self- evident, and to begin with the statement that registries are clearly necessary. I don't think this needs to be restated, but I think it needs some focus, and I do think that there was some consensus yesterday that there are probably three basic purposes to pregnancy registries.

The first is to identify the risks and safety, and safety is a very important consideration, as Sandy pointed out, for common pregnancy outcomes; to identify what I have called

major-risk teratogens. These include the classics, isotretinoin, or Accutane, and thalidomide; and to possibly identify signals for specific birth defects.

But while necessary, registries are not sufficient. Registries, even assuming an optimal design, are limited by their sample size. Birth defects, as we know, are a heterogeneous group of outcomes and include a wide range of specific birth defects.

And specific defects are rare events. Teratogens increase risks of selected specific defects, not all birth defects. Now, if a teratogen is sufficiently potent, such as isotretinoin or thalidomide, the increase in specific defects will reflect itself in an overwhelming increase in defects overall. But when you break them out, you'll find that there are selected defects which tend to account for that overall increase.

So a typical registry will have, just for argument's sake, about 300 exposed

pregnancies, and under the null, under the assumption that the drug in study has no adverse outcomes in terms of major malformations, one expects major malformations to affect 2 to 3 percent or, to give Lew his due, 2 percent, which would result in somewhere between 6 to 9 major defects overall in a population of 300 exposed women with no consequence of the drug. And this would include -- those six to nine would include a variety of specific defects.

So I want to consider two scenarios. One is false reassurance that might be provided by registry, and the other is signal detection. So for false reassurance, let's consider the scenario where we have 300 exposed pregnancy, and one observes the expected 2 to 3 percent outcome of major malformations, which would be, as I said, somewhere between 6 and 9 malformed offspring.

But let's assume for a moment that a drug causes a fourfold increased risk in oral clefts. The baseline risk for cleft palate -- or cleft lip and palate is roughly one in a thousand,

so a fourfold risk would translate to four per thousand. Under the null, no effect, one would expect, out of the 300, 0.3 cases.

Now, this is as complicated as any math I'm going to be presenting today, so try to follow me. But 0.3 cases is a little difficult to identify, so chances are you're going to see zero or one -- I think most people would agree with that -- out of, again this population of 300. So we would expect either zero clefts or one. But if there were a fourfold risk, you would expect four times as many, or 1.2 cases. Realistically, that would likely translate into one or two.

So the risk increase in this situation is simply lost in the overall observation of six to nine diverse malformations. So a statement of "No increase in the risk of birth defects overall" provides false reassurance about birth defect safety, since the studies failed to identify the true increase for a specific defect.

Now let's sort of flip the page and look at signal detection. So another registry, you

might see no appreciable increase overall, but, quote, "a signal is identified." For example, we observed three clefts overall where zero or one would have been expected. Well, that signal obviously requires testing in other datasets, leaving uncertainty for the sponsor, for regulators, prescribers, and, most of all, pregnant women. Testing such signals is costly and time- consuming, and many, or most, depending on your perspective, signals prove to be false.

So I want to give an example of a registry case-control situation that reflects some of the complementary approaches, and for this example, I'm using some published data that you'll see. And this reflects on the situation of SSRI antidepressants and persistent pulmonary hypertension of the newborn, PPHN, or as those of us of my age would remember it, persistent fetal circulation. Even defects get name changes.

So we're going back to the OTIS Pregnancy Registry that Tina Chambers and her group published back in the day, when they

followed -- early on in the introduction of the SSRI group of drugs, they followed 174 fluoxetine-exposed pregnancies. A hundred and one of those were exposed only during the first half of pregnancy and 73 were exposed throughout pregnancy. Those findings were published in a regional journal in New England, and there's the citation, back in 1996.

And not in the abstract, and certainly not in the title, and appropriately discreetly mentioned in the manuscript itself was this finding, that among the many outcomes examined, they observed two infants with PPHN where the expected would be one to two per thousand. So, you know, out of 174, 2 seems like a signal. And that was particularly intriguing since none of those two occurred in the mothers who took the drug only early in pregnancy, the first half of pregnancy. In fact, the two both occurred in the mothers -- 73 mothers who were exposed both early and late.

The finding, of course, lacks

statistical power and obviously was not statistically significant by virtually any test, but this small cohort offered a hypothesis, a signal, and that hypothesis was tested in our own birth defects study case-control surveillance program.

And, actually, we were engaged in a study specifically on PPHN because of another hypothesis relating to NSAIDs in pregnancy. But as we were formulating that study, Tina and her colleague, Ken Jones, brought to our attention the signal and said, you know, "You really must include a test of this hypothesis in your data," and we readily agreed to do that, and, in fact, Tina was very much involved in the analysis, as you'll see.

And in our study, in the case-control study, we had 377 extremely well-vetted cases of PPHN. And for those of you who are clinicians, you'll know that this is not an easy diagnosis to make. And we had 836 matched controls. I'm giving you the very short version. And we found

that exposures to SSRIs in the second half of pregnancy represented 3.7 percent in the cases and 0.7 percent in the controls, so the odds ratio -- the adjusted odds ratio was 6.1, with a lower confidence bound of 2.2.

And, again, for those of you familiar with birth defects epidemiology, 6.1 is a relatively large risk. We're used to seeing things in the order of 2 or 3; I mean, when we're not talking about thalidomide, Accutanes, and valproic acid.

What gave us some confidence that this finding had some validity was that we found no increased risk for early-only exposure, and we also found no increased risk for non-SSRI antidepressants. So that paper was published -- if I -- there we go -- with Tina as a first author, and the rest of us -- she and Ken were very much involved in the analysis, of course, and this was a study published in the New England Journal in 2006 based on the case-control data.

I think it's important to point out that

ten years elapsed between the identification of the signal and the first test of it. The finding has been subsequently corroborated by most other rigorous studies and a recent meta-analysis. And I think it's also worth pointing out that the analytic experience established working relationship between OTIS and BDS, a collaboration that has continued into VAMPSS.

And I think it's also worth anecdotally pointing out -- and I think Tina would agree -- that we used to consider our two study designs competitive. And I think as time went on and as we thought more about it, as we worked together, we realized that they both -- the designs both started with a C, but they really weren't competitive, they were complementary. And I hope you'll agree with me when you hear the rest of the information.

So what are the goals of this Vaccine and Medications in Pregnancy Surveillance System, VAMPSS? It's to provide a national systematic post-marketing surveillance system, something

which does not currently exist in this country; and to identify as early as possible the circumstances in which a drug or immunization causes harm; but at the same time, again, going back to Sandy's point, to provide reassuring data to all concerned for those drugs and immunizations, which are likely the majority, that are safe or relatively safe, during pregnancy.

The structure of VAMPSS is illustrated in this slide, and as you can see, the American Academy of Allergy, Asthma and Immunology, with Michael Schatz in San Diego as the PI, provides the infrastructural support for this activity, which has two research arms. The one on the left is the OTIS group, with Tina as the PI and Ken Jones; the case-control component at the Slone Epidemiology Center, with Carol Louik and myself; and an Independent Advisory Committee that includes representation from CDC, NIH, practitioner groups, a biostatistician, and a consumer representative. And I'll now give you a little more information about each of these arms.

So what is Quad AI (AAAAI), as we call it? It's the largest professional organization in the world of allergist-immunologists, and because asthma and allergy are so common in women of childbearing age, allergist-immunologists are often involved in making clinical decisions in pregnant women.

And the Quad AI(AAAAI) role in VAMPSS is not limited to allergy and immunology. And since Mike Schatz is not here, I will tell you that it was largely through his personal drive and leadership that this came about, his vision for something broader than just allergy and immunology issues.

And I think it's also worth pointing out it's the first professional organization that has taken upon itself -- Sandy mentioned the first drug company to take some initiative. This, to our knowledge, was the first professional organization to really dig its hands and get involved in a program that would provide information about the drugs that its member

practitioners used and worried about as well as their patients.

So they deserve a huge amount of credit, and the fact that they wish to continue to be involved in aspects of therapy that are not necessarily related to their discipline is only further evidence of their commitment.

So the research arm involves the prospective cohort OTIS arm, which I will go over relatively briefly, because I think we heard a lot about it yesterday, but just to give you the symmetry, this is a pregnancy registry study that looks at a variety of outcomes, which I will highlight, and it's run by the OTIS Research Center at the University of California, San Diego.

The case-control surveillance study, or the Birth Defects Study, provides birth defects surveillance, focused on specifically congenital malformations, and also provides exposure prevalence information, something that is badly needed when one makes requests for pregnancy registries. If drugs are simply not being used by

pregnant women, it's going to be very hard to assemble a registry of exposed pregnancies. And this activity is run by our group at the Slone Epidemiology Center.

OTIS, as you've heard, is a North American- wide network of university and hospital-based services, and it's been in existence since 1979. It provides service in terms of risk counseling to 80 to 100,000 pregnant women and providers, and they also have a very solid research activity, which collaboratively, excuse me, conducts prospective pregnancy registry exposure cohort studies, with a track record of productivity over 20 years and funding from government and industry.

Their research objectives are to evaluate the risk or safety of specific medication exposures in pregnancy, using the OTIS network as the primary basis for recruitment, and including, as we heard yesterday, an unexposed comparison group.

And here, just to highlight the outcomes

that fall within the purview of the OTIS studies, is the wide range of pregnancy outcomes: major birth defects overall, again, like any other pregnancy registry; spontaneous abortion; perinatal mortality; perinatal complications; birth weight; pattern of adverse outcomes. And, as Tina mentioned yesterday, they can engage in longer-term follow-up, as is appropriate.

I'm going to skip the infrastructure slides because you've seen that information yesterday, but the OTIS sites ascertain and refer potential participants to the Coordinating Center; exposed cohort, disease-matched cohort, and a healthy unexposed cohort are concurrently recruited; and all groups, through the same mechanism, receive multiple maternal structured telephone interviews at standard time points; and an outcome interview with medical record review; and in some studies, as Tina mentioned, specialized physical examination and developmental follow-up.

The maternal interviews and medical

record review provide detailed information. And I think this -- the importance of this can't be overstated, and I'll talk about this a little later. The dose, timing, duration of medication, and vaccine exposure -- and these exposures are coded using our Slone Drug Dictionary, so both studies use a common reference source, and this is a dictionary that we created specifically for pharmacoepidemiologic research, and a number of groups, including the CDC, use this dictionary.

Maternal disease or indication for the medication, so, as one of the speakers pointed out yesterday, it's extremely important to talk about potential confounding by indication. Pregnancy history, health history, demographics, and a wide range of potential confounders, including other prescription or OTC medications, BMI, tobacco, alcohol, and vitamin and mineral use.

The case-control study objectives, or the Birth Defects Study objectives, are to identify the risks and safety of the wide range of medications and vaccines with respect to specific

major birth defects and to establish ranges of safety for specific medications, where that information is available, and, again, to identify rates of exposure to specific agents. And this can be done in non-malformed controls and be very helpful and has proven to be very helpful.

The study was initiated in 1976, and, by golly, it continues to the present day. It's kind of embarrassing in many times -- in many talks to realize that many members of the audience weren't born when we started this. But, truth be told, we were very precocious, and I was about six years old, I think, when we began the study.

We've supported this study through funding from government and industry, and we have addressed many critical questions of risk and safety for many specific exposures in relation to specific birth defects; I mean, going back to Bendectin, for those of you, again, of a certain age.

The infrastructure is designed to provide a readily accessible database that would

be capable both of generating hypotheses regarding specific drugs and specific outcomes and also to test hypotheses raised by others. And it also was designed to be flexible to test new hypotheses so we can expand the case group, if necessary, to include outcomes that might not have previously been included, and we can expand exposure information.

Some -- many years ago, there was a suggestion that spermicidal contraceptives increased the risk of four groups of birth defects, and we were able to expand the information we were collecting on use of contraceptives to predate the pregnancy, because that was part of the concern.

DR. STAFFA: Dr. Mitchell, I'll need you to wrap up.

DR. MITCHELL: I'm sorry?

DR. STAFFA: I'll need you to wrap up. You're at 20 minutes.

DR. MITCHELL: Yep.

DR. STAFFA: Thanks.

DR. MITCHELL: The study subjects are infants with specific major malformations and infants without malformations who are identified at birth hospitals and tertiary hospitals and via state-based surveillance programs. And here are the two groups that I mentioned. And I will move along.

The mothers are interviewed by computer-assisted telephone interview by our own study nurses within six months of delivery, and the interview data, as mentioned before, include demographic/reproductive and so forth, and details of medication use, including prescription, OTC, vitamins/minerals and supplements and vaccine exposures from any provider, with medical record and vaccine record review and coding through the drug dictionary.

The limitations are potentially inaccurate exposure recall, because we are dealing with the mothers directly, and for OTIS, the concern would be accuracy, and for the birth defects study, the concern is both accuracy and

possible recall bias, although I would be happy to talk about the overblown concern about recall bias when you're using a very structured questionnaire. And spontaneous abortions are notoriously difficult to identify and study.

So what are the complementary strengths? The two studies together capture the wide range of pregnancy outcomes, including specific birth defects, and the registry provides a first line of defense to identify major-risk teratogens. The case-control arm provides an opportunity to generate hypotheses and test signals from registry and other sources. And the collaboration between the two groups, incidentally, provides additional scientific rigor.

The study subject is the final common pathway for all exposures. I think we need to recognize that. And our direct -- our joint direct- to-consumer queries, if we can use that term, can reflect actual exposures rather than prescriptions issued or filled and can also capture exposures via medication-sharing, which is

an increasingly recognized problem. And the interviews also provide information on critical confounders and risk modifiers. There's a list. The ones that are italicized at the bottom are the kinds of information that oftentimes can only be obtained from the subject directly.

Both studies were specifically designed to study drug and vaccine safety in pregnancy; decades of experience and hundreds of publications; and the findings are incorporated into product labels. Both are conducted contemporaneously and with academic independence of each of the groups; and rigor and peer review provided by an independent advisory committee. And that committee provides the kind of guidance that one would expect from a committee.

And I want to just point out that we have voting and non-voting members. The voting members are the ones you'll see listed, and non-voting members are sponsors. And this is one of the more active vaccine- focused advisory committees, and you can see that we have

representation from NIH, CDC, ACOG, the Academy of Pediatrics, and then we have two non-voting sponsors.

The VAMPSS program is an established public- private partnership. On the public side, we have government participation on the advisory committee, we have government funding. On the private side, the professional organization is the coordinator, the Quad AI, and we have professional organization representatives on the advisory committee and industry funding as non-voting advisory committee members.

In terms of our relationship with the FDA, the FDA has approved VAMPSS for meeting a number of companies' post-marketing commitments regarding pregnancy safety; the product-specific reports from VAMPSS are provided to FDA by the sponsors; and for selected other products, representatives of both CBER and CDER receive copies of VAMPSS reports.

So the final slide are VAMPSS projects, either active or under active negotiation. We are

currently studying influenza vaccines and influence antiviral medications, with support from BARDA, CDC, and CSL Limited, the Australian vaccine manufacturer. We are focused on a Menveo meningitis vaccine; asthma medications, with a focus particularly on long-acting beta agonists; and developing a protocol for duloxetine, under sponsorship by Lilly.

And under active negotiations are four drugs or vaccines, in addition to what's mentioned above, with -- and four companies, not necessarily these two overlapping, including some master services agreements which the companies are considering.

So with that, I will end, and thank you for your attention.

DR. STAFFA: Thank you, Dr. Mitchell. I'm going to ask, in the interest of time, that if you could jot down your questions, clarifying questions, for the end, we'll have a timeframe where you can ask those questions to the various presenters. But I'd like to move along.

Our next presentation is actually a tag-team. We will have two presenters about the MEPREP program. Dr. Susan Andrade will talk to us about the MEPREP program, and then Dr. Craig Hansen will be talking about the first study that was actually completed using that program. So Dr. Andrade?

DR. ANDRADE: Okay. Thank you. Again, this morning I'm going to be providing an overview of the Medication Exposure in Pregnancy Risk Evaluation Program, or MEPREP, and then I'm going to hand over the discussion to my colleague, Craig Hansen.

That's obviously not what I'm supposed to do. Before I begin, I just wanted to acknowledge -- okay. I wanted to acknowledge FDA funding for MEPREP. I'm really causing a lot of trouble here.

Again, my goal this morning is to provide a brief overview of MEPREP, concentrating on the datasets that we've created as well as the characteristics of the study population. And I'll

also be presenting some information on some activities of our program.

As you're probably all aware, health plan data is increasingly being used to study medication use during pregnancy as well as vaccine use during pregnancy. And by healthcare -- health plan data, I'm referring to insurance claims as well as records of healthcare delivery from electronic medical records, or EMRs.

Because the healthcare data or the prescription data are collected as part of clinical care, this avoids recall bias. And another potential advantage of using health plan data is the possibility to link to other data resources, which may provide information that's not available in the health plan data or is not -- is very incomplete in the health plan data.

And some examples include information on vital signs and laboratory test results found in electronic medical records and also information on gestational age at birth and race and ethnicity found in birth certificates.

MEPREP is a multisite, collaborative research program between the FDA, HMO Research Network, Vanderbilt University, and Kaiser Permanente, Northern and Southern California. The program is developed to provide a mechanism for collaborative research to address the safety of medications for use during pregnancy.

There are 11 distinct health plans, oh, within three FDA contract sites that participate in MEPREP, and these include the Tennessee Medicaid population; Kaiser Permanente, Northern and Southern California; and eight members of the HMO Research Network. This slide actually better presents the geographic diversity of the health plans, which are located in nine states across the U.S.

MEPREP currently has linked infant and mother data on women who delivered a live born infant from January 1st, 2001 through December 31st, 2008 and the children born to these women.

At the start of the development of the program, we actually put quite a bit of effort

into governance issues related to the organizational structure and study policies, but I won't be concentrating on these today; instead, I'll be concentrating more on the datasets and the data development.

And as far as issues related to data development, we had many decisions to make with the data extraction process, including identification of mothers and deliveries, linkage methods for linking the mothers and deliveries, and creation of the StudyIDs.

We also put quite a bit of effort into the data file specifications because, again, these were what were used to create standard datasets at each of the individual health plans.

As far as identifying mothers and infants and linking the information for the mothers and infants, this really varied across the different health plans. At the Kaiser California sites, the investigators used pregnancy registries that are maintained at the health plans. And because these two sites actually own the clinics

and hospitals where members receive care, pregnancy registries are believed to be very complete.

At Vanderbilt, the researchers actually obtained birth certificate data as part of an agreement from the State of Tennessee, and then they link this data to the Medicaid enrollment files using a probabilistic algorithm to identify the mothers and infants of interest.

And then, finally, the HMO Research Network sites used administrative claims to identify women delivering an infant. And this was based upon procedure and diagnosis codes. We then linked the deliveries of mothers to infants using different methods, including subscriber ID numbers or health plan identification contract numbers, name and address matching, and at two of the sites, we could also use birth certificate data to link the moms and babies.

The data model for MEPREP or data file specifications are actually based upon the HMORN's Virtual Data Warehouse, or VDW. And similar to

the VDW, the MEPREP sites have created files of enrollment, healthcare, demographic information, all in standard file formats which remain at each of the sites.

And even though these files are at the sites, programming activities are more efficient, only because we only need one lead programmer to develop the code where it plans to distribute to all the other sites that are working on a specific project. So the programming activities are both consistent and efficient, and the sites can retain the data rather than putting all the data in one central site.

We currently have nine files for the mothers and children in the program, and these include a linkage file, which includes StudyIDs for the moms and babies linked. We have files for demographic information, health plan membership information, pharmacy dispensings, diagnoses, inpatient stay dates and facility information, and procedures.

In addition to all these files, which

are created based upon the health plan data, we also have file for birth certificate data that has about a hundred different variables to capture data from the birth certificates. And then, finally, we have a file that links the patient medical record number or health plan identification number to the StudyID.

I know Dr. Hansen's also going to show this slide, so I won't go into this in any great detail, other than to know, again, all these files can be linked by a StudyID that was created specifically for the MEPREP program.

We actually now have about 1.2 million children born to over 900,000 mothers that were born between the period 2001 to 2008. About 43 percent of the population is from the Kaiser California sites, about 33 percent from Tennessee Medicaid, and 24 percent from the HMORN sites.

This slide actually shows the maternal age at delivery -- the distribution of maternal age at delivery in the MEPREP population and in the overall U.S. population of women delivering a

live birth for the period -- for the year 2005. And as you can see, the age distribution is actually very similar for MEPREP as compared to the U.S. population for a similar time period.

We have conducted a number of studies and analyses using MEPREP data. We've conducted a validation study of select data elements in the different datasets. And, again, I've given some examples here. We've validated gestational age at birth, birth weight, race in the birth certificate data, and we've also validated specific maternal diagnoses and congenital anomalies that we've identified in the health plan data.

We've conducted also a number of studies that have looked at the prevalence of use of specific medications and medication classes during pregnancies, and these have included antipsychotic medications, antiepileptic medications, antidiabetic medications, antiviral medications, asthma medications. And, again, we have another study that validated an algorithm used for gestational age assumptions. This slide just is a

list of the citations for the studies I've mentioned before as well as some descriptive studies that have used MEPREP data.

And now I will turn the discussion over to my colleague, Dr. Hansen, who will talk about systemic sulfonamide use during pregnancy and the risk of selected congenital anomalies.

DR. HANSEN: Thank you, Susan, and thank you, FDA, for having me here. I appreciate this opportunity. My name's Craig Hansen. Sorry. Whoops. Let me click -- thank you. My name's Craig Hansen. At the time of this study, I was an investigator at the Kaiser Permanente Center for Health Research in Georgia. I was part of the MEPREP team, so this was one of the major studies that had come through MEPREP, and thank you for the MEPREP team for having me lead this study. I'm currently at the Sansom Institute for Health Research at the University of South Australia.

So, first of all, I'd like to acknowledge the sulfonamide study team. As you can see, as Susan mentioned, it's 11 sites, so

it's quite large, in collaboration with a team from the FDA as well. So a big thanks to Susan and Katie Haffenreffer for being the backbone of this study and guiding myself and Heather Freiman, who was the project manager of this study, through the entire two-year process, which is very good. And also thank you to Elizabeth Maloney, for leading the FDA team and working side by side with her.

So today my talk is really just to give you an example of one of the studies that have come out of MEPREP, and I want to give you a very brief background of the sulfonamides, and then also -- which leads me to our study design, the rationale for our study design, and, importantly for this meeting, the logistics of conducting the established study using the MEPREP data, and then the strengths and limitations and challenges. Whoops.

So as you all know, sulfonamides are used to treat bacterial infections, such as urinary tract, respiratory, and skin infections.

It's estimated that about 2.5 percent of pregnant women are exposed to sulfonamides, which equates to about 100,000 births per year. Sulfonamides readily cross the placenta and act as folate antagonists. And as you know, folate is important for organogenesis.

It is still unclear if they -- if sulfonamides are teratogenic or not. There's been, over the past decade or so, about 15 studies published, and they have had mixed results, mainly because of different study designs, different case ascertainment, different exposure ascertainment as well. But what sparked the interest in this study, in the (inaudible) sulfonamide study, for MEPREP was that a recent study published by the NBDPS group at CDC looked at multiple antibacterials, and the sulfonamides had the highest number of -- significantly positive associations with birth defects, so they generated the interest of doing this for MEPREP.

We used a retrospective cohort study design, given that we're using administrative

data. It's, as Susan said, singleton live births between 2001, 2008. And then for the next three slides, I'll talk about the exposures and our inclusion/exclusion criteria and the congenital anomalies.

Whoops. Go back one. Thank you. So our main exposure was sulfonamides during the first trimester, and we wanted to come up with a comparator group -- two comparator groups, actually. Our primary comparator group was mothers exposed to non- teratogenic antibacterials during the same time periods, during first trimester. And we wanted to do that to try and reduce confounding by indication.

So we had decided to use -- after many long discussions, which I won't go into detail here, we decided to use penicillins and cephalosporins for our main comparator group. But given that many of the other studies hadn't done this -- they just look at non-exposed mothers versus exposed mothers -- we also wanted to have a comparator group that looked at the non-exposed

mothers as well. So the non-exposed mothers had no sulfonamides or antibacterials during pregnancy. And also we had a long list of exclusion medications as well, which I'll get to in a minute.

We did some -- a matching process here. We first of all identified all those mothers who had sulfonamides during the first trimester and then all those who had the non-teratogenic antibacterials as well. If they had both of them, they were excluded, because we wanted them to be mutually exclusive groups.

And then we matched them one to one, so one mother to one mother of -- one mother -- sulfonamide mother to one mother of the non-teratogenic antibacterials and also to one mother of -- sorry, one non-exposed mother, to create our two comparator groups.

This is a figure showing our -- all of what I was just mentioning then. So we have the top line, which represents pregnancy, going out 90 days prior to the LMP, the start of the pregnancy.

And our first criteria was to do with the mother's enrollment. That was a major criteria. So we wanted the mother to be continuously enrolled in the health plan, so we had all her information right from 90 days prior to the LMP right through to delivery. And the baby had to be at least a minimum of 30 days after delivery, continuously enrolled, if they hadn't died in that time period, although we did look for birth defects one year out from delivery.

And we have -- the mother -- first of all, after that enrollment criteria was put in place, then we had a medication inclusion/exclusion criteria. So if the mother had medications or vaccines, such as anticonvulsants, folate antagonists, iodine, thalidomide -- the list goes on quite long -- they were excluded at that point. And also, if the baby was born with a trisomy or varicella or rubella syndrome as well, they were excluded.

And then so the inclusion, as I stated before, sulfonamide mother during that first

trimester or a non-teratogenic antibacterial mother during that same period, and also a non-exposed mother during that same period.

And then the figure down on the bottom right-hand side, just so -- it shows three scenarios. So if the dispensing was prior to the LMP, but it overlapped into the first trimester, it was still classified as exposed. And then the other two scenarios are clearly in the first trimester. And I should just tell you that our exclusion list of medications is very long. We had many long discussions with FDA team about that. Whoops.

And for our outcome, our congenital anomalies that we looked at, we grouped them into five main categories that the other studies had looked at:

cardiovascular, cleft lip/palate, neural tube defects, limb deficits, and also urinary system anomalies. We looked at multiple -- a long list of anomalies within each of these categories, and then we grouped them into them. So that

figure is really showing that we looked one year using the ICD-9 codes from the administrative data. We identified potential cases one year out from delivery. And then we wanted to validate every single one of these cases, which leads into my next few slides about study design.

So we had a medical chart review done by a trained instructor, and also it was adjudicated by physicians who had expertise in this field as well, and then that way, we came to knowing whether they were a confirmed case or not. I'll talk more about that on the next few slides. Sorry if this is a little small, but this is our schematic diagram from our manuscript that we're hoping to get published soon.

So -- let me see. This is -- I don't want to go into this in detail because we don't have time, but it's really showing how we got to the final cohort that we analyzed. So we start out with roughly 1.1 million babies, and then after the inclusion criterias or enrollment criterias, we end up with just over five and a

half -- 500,000, sorry, potential people for the study.

And then from that, you'll see here we identified 10,000 mothers with sulfonamide exposure during their first trimester, 63,000 of the non- teratogenic antibacterials, and roughly 400,000 of the non-exposed mothers. We excluded just under two and a half thousand mothers who had both a sulfonamide and non-teratogenic antibacterial.

So that left us with around 6,000 -- 7,615 sulfonamide used during the first trimester. Then we did the matching process from that, and we ended up, and there was one excluded -- one infant excluded because it had trisomy, after the chart review was performed. And then we ended up with a cohort of 7,614 sulfonamide users. So we had that same amount in each of our two comparator groups because they're matched one to one.

And then our final analyses, there were some -- we ended up with 6,000 -- down here, 6,698, because we wanted to use everyone who had

complete data on all the covariates. Whoops.

So why did we use this study design? Why not a typical case-control study? And as I was just saying, we wanted to validate every single birth defect in here. So if we had chosen a case-control design where we had looked at all the cases within our cohort, then if we have a 3 percent prevalence, roughly, out of the million babies, you're looking at 30,000 cases. Even if we drop it down to those who met our inclusion criteria of around 500,000, you're looking at 15,000. And then even if you drop it down further with only the 7,000 or drop that down half again, you know, you're looking at 15,000 cases or so, or 7,000 cases.

So we -- because of the funding and the timing of the study, we can't actually validate all of those cases, of course. So then we decided for the alternative, which is the retrospective case-control, where we could actually validate all of them. So we looked at their exposures first and the cases among those exposed and non-exposed.

We could have done a 10 percent random sample, of course, but that means some of those cases are going to be false positives.

What we ended up with was out of our 20,000 or so in our final cohort, we ended up with provenance of around 4 percent of potential cases, so we were close in the ballpark there. And these two diagrams down on the bottom of this slide here, they just show the difference. There's a bit of trade-off here. Obviously, neither design is the best design, but if you look at the left-hand diagram, it's the typical case cohort study, which is what we used.

So we could have captured all the sulfonamides, but then on the downside of that, we have fewer birth defects, but we are able to validate all of them. So we have true positive birth defects, but we have less statistical power. Then the trade- off on the other side of that -- the upside is if we have all birth defects from a case-control study, but we only validate a sample of that, then we're going to get false positives,

and also we don't get all the sulfonamide-exposed mothers. So you can see there's a trade-off between the two different designs here. Whoops. Next slide.

I'd like to just finish up now. The second half of this talk is really about the logistics of conducting such a study using the MEPREP data -- the administrative data. So as you know, it's 11 participating sites. Each site has a PI, a project manager, a data programmer, abstractor, and an adjudicator. So it's quite a large team that you have to manage when you're doing one of these studies.

And the typical tasks for any type of study like this, you have to get IRB across all sites, data use agreements, because we had -- we were lucky for this study. We actually -- the lead side, which was my side, we received individual-level data for this study as opposed to aggregated data, which is often the case in these distributed multiple-site studies. So we spent a good, solid amount of time working with FDA on our

study protocol at the very beginning. We performed initial data extraction to look at all the data first while we're doing that study protocol as well.

Then after we identified those with the potential birth defects, we performed the medical chart review at each site, and then we went back and did a final data extraction on all the other information we wanted on them and the usual process of cleaning the data, analyzing the data, and the final reports and manuscript to the FDA. So there's a lot involved. We did this in two years.

This was a part of Susan's slide before, just showing the dataset structure, and it's your typical workflow. I'll go into this on the next slide, actually. So I just want to give you two examples of workflow process that you have to consider when doing these large, multi-site studies. You know, for the data programming, the lead site, we develop the SAS code, and then we test it on two beta sites, see if it works

properly on their data as well, and then we make any revisions. Then we send it out to all 11 participating sites. They run the code.

And the beauty of using MEPREP data is that we have such fast turnaround. We -- for the what we call a work plan here, we would have a turnaround within two to three weeks of them getting the data back to us, which is very fast, because all this data is set up, and it's standardized already.

And then -- whoops. Go back one, please. And then we have the medical chart abstraction process as well. Overall, this took about six months in the middle of the study. Well, the first -- after the six months of the study. This took six months. So this was one of the biggest challenges as well.

We developed a chart abstraction manual and database, and I'll thank Jan Cragen for helping us on that and her team of abstractors at the CDC. And we had to train our abstractors as well, using our database and our manual, and we

got feedback from them, and then we made modifications on that. And then after that, they did the chart abstraction at each of those sites. So that took six months.

Next slide. So the strengths of using MEPREP data or administrative data like this, so first of all, it's -- the exposures are based on pharmacy dispensing. So we can get the timing of the exposure almost spot-on there from when it was dispensed, and we have no recall bias. We didn't have to interview mothers six to twelve months out from delivery wondering what medications they're on during the first trimester. So that's a major strength of this.

And also, because of our large sample size to start with, we could apply a really strict exclusion criteria. And as you saw based on the enrollment, say, out of the one million or so, we ended up with 7,000 sulfonamide mothers because we had strict exclusion.

And the -- as Susan showed in her presentation, all the MEPREP data or standardized

data are readily available at each site, so we can run these studies very fast. And for future studies, we can not only look at outcomes during perinatal period, but also long-term follow-up. Because this cohort now finished in 2008, it's now 2014, so we -- they may be six, seven years old, the youngest ones in the cohort, so we could follow them for that time period.

But like any study, there are limitations, of course. The main limitation that we get asked, we don't know if the mother actually did ingest the medication or not. But given that we looked at the antibacterials and the mother's desperately wanting to clear out that infection, we can pretty much assume that she did take these particular medications.

It is limited to only outpatient medications, so we don't get inpatient or over-the- counter medication use. We do have limited information on some of the potential confounders, like smoking or alcohol use. The variables are there, but there's a large percent of missing data

on several of them, but that's limited to only a handful of variables.

And in this particular study, we had reduced statistical power. We had too few many cases to examine individual birth defects, so that's why we grouped them into these five main groups. We also didn't ascertain the cause of death, if the baby had died in that one year after delivery, and that way we didn't know if it was from a birth defect or not. And that's the next point down there as well, it's only live births, so if there were stillbirths, we didn't capture that. Next slide, please.

And then the last slide -- second-last slide, the challenges and lessons learned from this, so as you can imagine, organizing tasks across 11 sites within a very large study team. You have to be extremely organized to keep it all going and keep on everyone's back to make sure they keep up with the pace of the study.

The medical chart review, that was the most time-consuming of the entire study, as you

can imagine. Avoiding study creep, this seems like very basic thought, but it happens. When you're working in large studies, large studies with many PIs and they all have their input, you can sometimes start veer off track, and you've got to pull them back a little bit.

This is a very basic one too, but it's extremely important, a timeline. Develop that timeline that is flexible. So we had a very good timeline set up, but there were periods when we had to go back a few steps and then go -- re-gather ourself and then move forward again.

And transparency, this is extremely important, I've found, keeping everyone up to date, because my job as the lead PI at this site was to run the study so I knew what was happening every step along the way, but you want to make sure all the other PIs and the FDA team know what's happening in every way. And I get to look at the data every day at my computer, but they don't, so I need to find out the best ways to give them the insight that I would have without looking

at the actual raw data.

And lastly, MEPREP, it's an excellent source of data for future research in this area. And one more slide. Thank you. And this is a joint slide from Susan as well, potential development into full- scale program, looking at different mechanisms and funding at the moment. As Susan mentioned, there's a potential of linking datasets to other external datasets: death certificates, cancer registries, and also vital signs, et cetera.

I've already mentioned this one as well, potential to identify additional pregnancy outcomes and also potential partnership with additional sites to increase the sample size as well. So I can see MEPREP going forward in that area.

Thank you. That's all.

DR. STAFFA: Thank you, Drs. Andrade and Hansen. Again, if you can jot down your questions and hold them for later. Our next speaker is -- our next talk is also going to be a tag team

approach. We will have two presentations from the Department of Defense on two different data systems that may have some potential for being complementary to each other. And I believe our first presenter is going to be Dr. Conlin, who will then be followed by Dr. Coster. Is Dr. Conlin going to be speaking first?

DR. COSTER: Well, actually, (inaudible).

DR. STAFFA: Okay.

DR. COSTER: (Inaudible).

DR. STAFFA: Perfect.

DR. COSTER: So

DR. STAFFA: So, Dr. Coster, you'll be starting us off? Okay. So Dr. Trinka Coster from Department of the Army will be starting us off, and then we'll be moving -- Dr. Conlin, I just want to make sure you are indeed on the line?

DR. CONLIN: I'm here. Can you hear me okay?

DR. STAFFA: We hear you just fine. Just sit tight, and Dr. Coster is going to start

us off. Thank you.

DR. COSTER: Okay. Our disclaimers for -- our opinions do not represent those of the Department of Defense and all the other services, and for nondisclosure, for financials is none for the Pharmacovigilance Center, since we collaborate with the FDA as well as with our formulary deciders. We do not work with the pharmaceutical industry unless the Surgeon General is the sponsor.

I'm going to give you a quick overview of the Medical (sic) Health System, which is a little bit confusing, and then, as you heard from Dr. Conlin, she'll be talking about the DoD Birth and Infant Health Registry, and then Dr. Thelus will be talking about the Mother-Child Database that we developed for drug surveillance, with input that we received from MEPREP, and then conclusions.

So for the MH -- let me just go -- see if I can go back. It's a little bit confusing. We basically provide care for our active duty

service members as well as their dependents as well as retirees and their dependents. We have all seven services that can visit our health systems, but most people think of Army, Navy, Coast Guard and Marines and Air Force.

We have two systems. We have our direct healthcare system, which is supported by a electronic health record, so both inpatient and outpatient health records. So we have -- this care is provided at 60 hospitals throughout the United States and other parts of the world as well as 400 health clinics. We receive inpatient ICD-9 codes and CPT codes from those records. We also have inpatient and outpatient CPT and ICD-9 codes.

In addition, we have access to vital signs, labs, rads, and path reports, as well as ability to easily do chart reviews. In addition, we have a whole Tricare health plans for purchased care, so there's multiple plans that people can get both as active duty, beneficiaries -- their beneficiaries, as well as when they retire. And on those, we just get the claims data. So on

those, you get the inpatient and outpatient claims, but you do not get the labs, and you do not get the inpatient medications.

An emphasis on the direct care or medical treatment facilities and on the civilian purchased care, for the pharmacy data, you get all purchased pharmaceutical information as well as that that's dispensed by mail order as well as that that's dispensed in our own pharmacies.

On the direct care side, we do get inpatient pharmaceutical information. What we do not get is those pharmaceutical products that are delivered in the emergency room and those pharmaceutical products that are delivered in the operating room. Those are separate standalone systems that do not feed into our pharmaceutical transaction systems.

This kind of shows you a little bit of difference between the MHS population and the U.S.

population. You can see we're a little bit young, and then you can also see that our retirees are a little bit more robust than the

U.S. population, a slightly different distribution of males to females.

For the eligible female population, we have -- you can see that our Army is the largest service, and so, hence, you find the largest distribution of eligible females, and comparing the active duty to non-active duty, it's about 11 percent are our active duty service members, and the majority, hence, are non-active duty.

And then on that, I'm going to turn it over, because we're short on time here, to Dr. Conlin. And is somebody going to be advancing for --

DR. CONLIN: Good morning, and thank you for having me today. My apologies that I can't be there with you, but I thank you for the opportunity. Next slide, please. I'd just like to (inaudible) Colonel Coster, and we are supported financially by the Department of Defense, and some of our active registries are sponsored by -- in particular, our anthrax registry by Emergent BioSolutions, a manufacturer.

Next slide, please.

So the Department of Defense is challenged with monitoring and protecting the health of our service members and their families. And really dating back to the first Gulf War experience, it became evident that service members and policymakers and military leaders had a concern that there was potential exposure during that period of conflict that could have led to some reproductive health concerns. These might be related to deployment or the fact that our military service members are located throughout the world in many geographically diverse locations and that they receive some compulsory vaccination, mainly smallpox and anthrax vaccines.

As you know, there are more and more women in the military, which highlights the need to really focus on them with these military-unique exposures, especially now that they will be assuming some additional military occupational specialties and have some unique exposures. And the existing civilian registries, because of the

geographically diverse population located not only throughout the U.S., but throughout the world, still makes it difficult for any civilian registry to accurately assess these issues among military families. Next slide.

The Department of Defense Birth and Infant Health Registry is a retrospective assessment of birth defects and other adverse infant health outcomes, and we were established way back in 1998 by the Assistant Secretary of Defense for Health Affairs. And then in our reproductive health portfolio, we also have two active pregnancy registries, for smallpox vaccine and anthrax vaccine. Next, please.

We are conducting surveillance for birth defects among all of our healthcare beneficiaries, but in addition, we are now able to look at some other indicators of infant health, such as preterm birth and birth weight, growth problems in utero or in infancy. We do monitor the male/female sex ratios and overall assessment of population health, and we've done some work looking at

neoplasms in infancy.

Also, the registry is limited to live births. In recent years, we've also been able to include pregnancy outcomes, including losses, among particularly our active duty beneficiaries, who may experience a specific exposure concern, until we feel we have particularly complete prenatal care data in order to assess the timing of their pregnancy and their outcome. Next slide.

We're using a lot of the electronic medical record data that Colonel Coster referred to from the MHS Data Repository. That includes ICD-9-CM codes from both inpatient and outpatient healthcare encounters at military and civilian care facilities.

We then use extensive algorithms to identify these live births and infant outcomes. As I mentioned, we're now looking at pregnancies and pregnancy outcomes as well. We do include data through the first year of life for all of our infants, and now there's protocol approval to go up through early childhood, age five.

We are then able to link to parental demographic and military exposure data that may include vaccinations, may include deployment, geographical location, military occupational specialty. And then oftentimes, we're able to link to some other self-report data that military service members may have completed in some surveys.

We identified each infant, and currently we do exclude same-sex multiples because of the overlap of their data in the electronic record. Next.

Our data dating back to 1998 through complete data for one year of life through 2011 show that we have 1.5 million beneficiary infants, and we include over 1.4 million of those in our ongoing analyses. Over time, the excess of births that we've had, more than 100,000 per year have been happening out in the civilian sector, that purchased care, as Colonel Coster referred to it, so now overall, we have (inaudible) majority that are being born in a civilian institution.

Between 15 and 16 percent are born to our military mothers. This is important because we have more information about the active duty military mother than we may have about the dependent stepmother married to an active duty military man. They tend to be young women in our mid-enlisted rank personnel, and, as I mentioned, in all 50 states and foreign countries throughout the world.

And about 60 percent of our infants do remain continuously enrolled in the system through age five, providing a large cohort of infants to do additional studies later in childhood. Next slide.

Our birth defects are defined by the National Birth Defects Prevention Network guidelines. We do require one inpatient or two outpatient visits on different days to consider them to be a valid defect, and that's been proven to be effective using our validation techniques. And, like I said, we do look at birth defects diagnosed throughout the first year of life.

Next.

Our overall prevalence of birth defects is 3.6 percent, and as you might expect, the most commonly diagnosed are some congenital heart defects as well as genitourinary defects. Similar to what we see in the published literature, this prevalence increases with multiple gestation, among our male infants, and with increasing maternal age. We do not, however, see a difference between our military mothers and dependent wives, nor would we look at individual military occupational specialty code. This is reassuring overall and consistent with what we see in civilian data. Next.

This is some of our registry findings that we've had over the year. We publish our disease prevalence in the Birth Defects Research Part A each year. Most recently, we completed an H1N1 vaccine in pregnancy study and were able to do that in a relatively timely manner because of the availability of our data, and that was our first effort where we looked not only at live

births, but also at pregnancies among our active duty women.

We've looked at birth defects in infants born to folks who served in the Gulf War era somewhat remotely in time, looking forward 7 to 14 years. Next. And we've always looked at some military-unique exposures recently to look -- and to include the open- air burn pit that our service members were experiencing during combat.

We've done a number of methodological validation studies -- next -- and spent a good bit of our time looking at reproductive health outcomes following military-unique vaccinations, including anthrax vaccine and smallpox vaccine. Next slide, please.

Currently, we're looking at the safety of Human Papillomavirus vaccine in pregnancy and also safety and effectiveness of the Tdap vaccine in pregnancy. We'll also be starting some work looking at anthrax vaccine immunogenicity in pregnant women. And some other military-unique exposures that we're looking at include the

TOMODACHI experience following the earthquake and tsunami in Japan. We continue to do validation work, comparing our data to birth certificate data from selected states, and we have ongoing collaborations with DoD, federal, and state agencies and do a number of residency collaborations to help our residents at our military treatment facilities meet their research requirement.

We are looking at potential collaborations with both the Organization of Teratology Information Specialists, who you heard from today, and we've been trying for some time to perhaps be more involved in the Vaccines and Medications in Pregnancy Surveillance System. That takes a good deal of collaborations from the higher-ups in our Department of Defense system. Next, please.

Our surveillance is primarily limited to live births, and we're not looking at birth defects from early pregnancy losses, abortions, or stillbirths, but we are now able to look at

pregnancy losses when we have a defined maternal population. Like many of these types of registries, we cannot describe the constellation of defects and severity of defects based on the limitations of the ICD-9 codes, but our validation efforts continue to verify the quality of our data, and our ability to link to environmental and occupational exposure data, particularly some of the military-unique exposure data, is a tremendous asset of the registry. Next, please.

I didn't want to spend too much time on this, but did just want everybody to be aware that we are also the folks that are doing the National Smallpox Vaccine in Pregnancy Registry and have been doing that since 2003. Next, please.

Women are referred to this registry in a standard active registry type model for exposure before pregnancy or throughout pregnancy. Next, please. And we're currently following over 500 women in this active registry.

Overall, the prevalence of birth defects is 2.8 percent and preterm birth, 4.7 percent in

this cohort. Lots of discussion that we could have on this as to the reasons why, (inaudible) enrollment, many things that were discussed yesterday, but we can save that for another time. Next slide.

And, finally, our BioThrax Anthrax Vaccine in Pregnancy Registry was just established back in 2012. Next, please. Similar methodology to our Smallpox Vaccine in Pregnancy Registry, one unique difference being we did not require consent for our smallpox registry because it was initially established as a public health response, whereas consent is required for anthrax. And you can see the impact that has in enrollment on the next slide. We are currently at 35 subjects that have enrolled, with 18 birth outcomes for that. We'll be continuing to enroll for that registry over the next several years. Thank you.

DR. STAFFA: And now I believe Dr. Thelus will continue?

DR. THELUS: Yes, thank you. Sorry for all the different transitions. For this part of

my presentation, I will focus on primarily talking about the methodologies that we used to compile our Mother- Child Database housed at the Pharmacovigilance Center.

So the overall arching goal and background information presented by Dr. Conlin regarding the DoD Infant and Mother Registry and the purpose for setting those up is relevant to her presentation here as well. So in order to avoid redundancy, I'll primarily be focused on some of the methods that we have outlined to identify mothers, pregnant mothers and different outcome.

So the Mother-Child Database is housed within the Pharmacovigilance Center and was initially funded by the FDA from October 2009 to 2012. The primary goal of the funding was to develop a mother- child database linking pregnancies to birth and the other pregnancy endpoints that would allow for rapid drug assessment as well as feasibility of drug adverse event associated with medication use before,

during, or after pregnancy.

As previously presented, the DoD population contains a unique group of active duty and non-active duty women of reproductive age. And other than the work that Dr. Conlin has done related to birth registry and specific outcomes, little information is really known about medications and -- medication use and pregnancy outcome in this population. Therefore, it's really important for us to understand and monitor such information in this population in order to provide actionable information to our military leadership and in order to improve the lives of both our active duty population and their family members.

So prior to embarking on compiling this Mother-Child Database, we conducted thorough review of the literature, and we settled on using an algorithm similar to the one used by Devine and colleagues, in order to identify pregnancies.

In addition to this algorithm, we also developed methods to link children and mothers,

using unique pregnancy IDs that -- Colonel Coster mentioned that we do have two systems of care, so from our military treatment facilities, births that occur in our military treatment facilities, we can link them to unique pregnancy IDs. We also develop algorithms to link pregnant women to other pregnancy endpoints as well as consulted with several subject matter experts from the DoD as well as from the FDA.

Dr. Pamela Scott, who's actually one of our panelists, was instrumental in providing key insight from her experience of having worked with the MEPREP data and setting up our database.

As described by Colonel Coster, our data sources confirm two different competent of care provided. In these components, all the data files are housed within our Military Health System Data Repository, and these consist of demographic information, enrollment information that allows us to see how long the women are enrolled for, sponsor information. We also have access to drug information dispensed, encounter, inpatient, and

outpatient information. These datasets are extracted on a quarterly basis from the NDR (ph) and uploaded to our PharmacoVigilance Defense Application System and transform in a way that allows us to identify pregnancies, like these pregnancies to child and other birth outcome, and obtain final database that we can use either for rapid analysis within the PVDAS application, or we can use it to link back to drug information as well as encounter information to do full epi (ph) analysis, where we can identify additional confounders, to include if we were to take on -- if we were to move on to the next step.

The PVDAS is a unique platform that allows for automated drug utilization analysis in our overall population, and with the finding that was provided from the FDA, we were able to actually update and configure the current system to run the algorithms to create the mother-child database and allow for the same functionalities that we can currently use in our overall population.

So within PVDAS to create our mother-child database, we are able to identify our eligible population based on monthly enrollment information, and then the inpatient and outpatient encounter from both system, from a military treatment facility as well as outpatient, are transformed into a common data model.

Drug files are enhanced with additional inputs from First Databank, and then we incorporate additional dataset to enhance capture and validity of our pregnancies identified as well.

So there are four major steps in identifying pregnancies within PVDAS, and the first thing that we did was to identify end of pregnancy indicators and -- through a list of ICD-9 and CPT code. And I will go over that a little bit more detail as to how this occurs in our system.

Second, we match live births to pregnancy based on child's date of birth. Sometimes we do have potential data conflict that

arise when your end of pregnancy codes may indicate multiple outcomes and are flagged, and we have different ways of dealing with these conflicts.

The third step is that we determine gestational age and estimate date of conception. The date of conception is typically based on subtracting the end of pregnancy -- the date of the end of pregnancy indicator minus the gestational age. For live births, if we have a five-digit codes, we usually have -- we usually use that as an indicator of the number of weeks, and then we subtract that from the EOP to get an estimated conception date.

For live births where we do not have the code, we typically use a default, and that default can be altered or changed as necessary by the user, as you'll see in the next slide. Stillbirth and miscarriages can also be specified using default pregnancy duration.

And, finally, we establish pregnancy care period using algorithms to create a start of

pregnancy care date using codes from pregnancy care indicator list.

So, briefly, I will take you through how the mother-child dataset is actually set up. In the first step, we select pregnancy care indicators, and this could be -- you could specify either drugs, ICD-9 codes, or CPT code.

In the next step, the user has the option to specify a list of end of pregnancy indicators, with the same options given, where you can specify the drug ICD-9 code, CPT code, as well as lab information can be specified.

So the first thing that we do is specify codes for live births, and then the same window appears where you could specify codes for stillbirths as well as miscarriages and abortion. I should mention that for miscarriages and abortion, we rarely see -- for abortion, we rarely see some of these codes, just because the DoD does not cover for elective abortion.

So we also have a set of rule-out indicators, so rule-out indicators are instances

where you see, during the time period where you examine pregnancy indicators, you may see a woman being dispensed either a prescription for birth control or having an encounter for prescription of oral contraceptive. So if that's the case, that could be a rule-out, and you would flag that information so whenever you're analyzing the dataset, you could choose to include those observations or not.

And then in our final window is really where you have the option to either keep some of the default parameters, or you can change some of the parameters. So you could specify the minimum interval required from the end of one -- from the end of the pregnancy to indicate a separate pregnancy. And currently, our default for stillbirth and live births are about 210 days. And then you could also specify the minimum interval between your start of pregnancy care and your end of pregnancy care to require that a pregnancy is fully characterized.

We also have some other -- some

additional indicator regarding the duration of pregnancy when no other information is given regarding the gestational age. In this window, you can specify specific ICD-9 codes with their respective gestational age that can then be used to estimate start of pregnancy.

And this is -- sorry, my timer is up. This is an actual patient timeline that I think is very nice to be able to actually visualize some of the competent that is actually occurring during the pregnancy.

So you do have the option, once you generate the database, to drill down into one specific patient and see what is going on during the specific trimester; what types of drugs do they have, what types of procedures do they have, and this is just for exploratory analysis, if you were interested in a specific set of group and you wanted to gain some additional insight into what's occurring during the pregnancy.

Briefly, I will just touch on some of the most recent numbers that we've gotten from our

most recent run from 2005 to 2011. So our total number of potential pregnancies, about a hundred and .4 (sic) million women, and of those, about a million -- about an equal amount have at least one EOP and at least one SOP.

Overall, there's about 60 percent of all potential pregnancy that have both an SOP and an EOP with no data conflicts. Of these pregnancies with no data conflict, about 87 percent of them ended up in live births, and 88 percent of them were subsequently matched to moms, which is pretty high when you're looking at the numbers in some of the -- some of the absolute numbers, so you have about 636,000 women that are available live birth match for analysis, if you wanted to do drug utilization analysis.

And I'll just briefly say these are two of the recent analysis that we conducted. So I believe Dr. Greene presented some information about some of the recent hot topic, talking about neonatal withdrawal symptoms, and we wanted to see

if we could correlate some of this information with trends that's occurring in the mom while they're pregnant. So we did some of these analysis for opiate used by trimester, and we also conducted an analysis on NSAID.

Because we're running out of time, I'm just going to skip over this, and if you guys have additional questions later, I can address those. I think some of the strengths and limitations are very similar to what other presenters have presented, so I won't dwell too much on that, but one thing I do want to note is that we do have a large number of pregnancies that are available for analysis. And I think our dataset -- our database is unique in that it can complement some of the birth registries and some of the information that we've talked about.

So prior to embarking on setting up a registry, you could definitely look at certain prevalence exposures, incidence exposure in that specific population to gain additional insight into how to set up or what specific approaches may

work or not work.

And these are just our acknowledgement, and now I will leave it up. I'm not sure if we have time for questions.

DR. STAFFA: Thank you, Drs. Coster, Conlin, and Thelus. So I hope you're jotting down all of your questions. At this point, I'm going to use the Chair's prerogative to rearrange things a little bit. We still have two speakers to go in this session, and I'd like everybody to be able to listen to them, so I'm going to take a quick ten-minute break, but I'd like to be back here in ten minutes. So that is what time, Vicki?

MS. MOYER: Seven --

DR. STAFFA: It's 10:07. So we'll be starting again promptly at 10:07. And did you have some other announcements to make?

MS. MOYER: Yeah, so if you're a panelist and you were interested in a box lunch, which you previously arranged, please see the kiosk. Anybody else who wishes to purchase a sandwich at the kiosk may do so. You may want to

do it now instead of later. And please, again, come back at 10:07 so that we can start and finish our day. Thank you.

DR. STAFFA: Thanks.

(Whereupon, a break was taken.)

DR. STAFFA: Welcome back. We're going to get started. I wanted to thank you for your patience with some of the scheduling changes we're making. These are all wonderful talks, but as you can tell, we're trying to get a lot of information into a short time period, so we want to take best advantage of that.

I wanted to make sure -- our next speaker is doing to be Dr. Allison Naleway from Kaiser. Dr. Naleway, are you on the line?

DR. NALEWAY: Yes, I'm here.

DR. STAFFA: Wonderful. Well, Dr. Naleway's going to be talking to us about the Vaccine Safety Datalink. And, again, we'll be starting, and, Dr. Naleway, I'll ask you to be conscious of the time. If you could try to stick to your time as close as possible, that'd be

great. So go ahead, Dr. Naleway.

DR. NALEWAY: Okay. Thank you, and I'm sorry that I can't be there in person today. I managed to come down with a pretty nasty respiratory virus and got placed on the no-fly list by my doctor. So if you want to go to the next slide.

My disclosure statement, I have received some research funding from GlaxoSmithKline. Next slide, please. So this is just an overview of the Vaccine Safety Datalink. It's a collaboration between integrated care delivery systems and the Centers for Disease Control, and the project's been around since 1990.

And basically, we pool our healthcare data weekly, and we also pool them annually to support vaccine safety surveillance and studies. And like we've seen with some of the other studies today, the dataset resides with the sites, and they're accessed remotely by CDC and other investigators.

So the datasets we've built include information about member demographics, their health plan enrollment, diagnoses and procedures, and, of course, vaccines. And we supplement these files with birth and death certificates, where available. Next slide, please.

This is a map showing the distribution of the VSD partner sites. And you can see we have pretty good geographic representation. About half of the sites are Kaiser Permanente sites, and the other half are not. Next slide, please.

So about five years ago, we started thinking about doing vaccine safety studies in pregnancy within the VSD, and we formed a working group. And our opinion on this was really prompted by some of the recent outbreaks of H1N1, pandemic influenza in particular, and some of the new vaccine recommendations for pregnancy, and thinking about Tdap in particular there.

And as we formed our working group, we recognize that there's really very little scientific evidence about vaccine safety during

pregnancy that could be used to inform vaccine recommendation. And as our workgroup sat and talked, we identified three key challenges to doing vaccine safety during pregnancy work within the VSD, and the first was how to identify pregnancies and outcomes and dates of events with our dataset, how to link mothers to infants, and how to collect important information on other covariates. And these are really similar themes to the presentations we've seen already today. Next slide, please.

So in terms of identifying pregnancies and outcomes and dates, we picked the approach that we wanted to identify not just live births, but other pregnancy outcomes. And we had some real interest in looking at spontaneous abortions in particular.

And there was an algorithm developed by Mark Hornbrook here at my site, Kaiser Permanente Northwest, with the CDC, for a project called the Maternal Morbidity Project. And I'm not going to go into too much detail about this because the

previous speaker, Dr. Thelus, just covered this in great detail.

The Hornbrook algorithm was adapted to also run in the UK General Practice Registry Dataset, and it looks like the DoD's actually adopted this algorithm pretty much the same way that we're using it. So her presentation just had a lot of nice detail in it, so I think I can skip over some of that here.

But you could tell from her presentation that this algorithm uses a lot of data. It has laboratory test data and pharmacy data and ultrasound reports. And those additional data inputs are just not included in the standard VSD dataset.

So in the Hornbrook algorithm, they had very good agreement with medical records for identification of pregnancy outcomes and dates and gestational ages. And our challenge really was could we take this algorithm and scale it down to work with a VSD dataset that we create on an annual basis? Next slide.

So we took this Hornbrook algorithm, and we scaled it down, and we really focused it on just identifying pregnancies using ICD-9 diagnosis codes and CPT procedure codes. And then we also -- as I said earlier, we incorporate birth certificate data into our VSD files.

So the VSD algorithm will use the gestational age data from those linked birth certificates when it's available, and then when that gestational age is not available, it just estimates -- the algorithm will just estimate the gestational age. And those are based on published averages, which the last presentation covered. And you can adjust this, again, within the confines of the program. The next slide, please.

And, here, I'll just kind of skim over this, because, again, it's the same basic model for this algorithm, and people are always like, "Well, what is this algorithm?" It really boils down to a program that was written in SAS (ph). It's a very complex program and a set of tables, lookup tables that have a whole bunch of codes in

them from looking at pregnancy outcomes, endpoints, and other types of exposure. So that's all I mean when I say an algorithm.

So this algorithm or this program will search through our VSD data files and look for any pregnancy indicators, like ICD-9 codes or CPT codes, and then sort also through a hierarchy to determine which will best indicate a pregnancy end date and outcome type.

Just for example -- and I think the previous presenter gave some good examples of this too -- like the algorithm will look and say, well, if you have a code for a miscarriage and you have a code for a live birth, and they're only one month apart, which one should you consider to be the truth for that pregnancy episode?

So after the program identifies the end date and the outcome, it will go through a second hierarchy to assign a start date to the pregnancy. And, again, if the gestational age is available from the birth certificate, it pulls that in. If it's not available, it estimates that. And then

our algorithm will spit out a new file, which we call the pregnancy episode file. Next slide, please.

And the pregnancy episode file within the VSD is a really simple file. It's got the mother's StudyID number. It has a variable that indicates the pregnancy outcome type, if it's a live birth or spontaneous abortion. We do identify elective abortions, stillbirths, ectopic pregnancies, et cetera. And it'll also give you the pregnancy end date and the pregnancy start date. And that's all that's contained in those files, and then we link those into, as I said, some of our vaccine files and our diagnoses and procedures files. Next slide, please.

So we have done some validation work with the algorithm. We identified close to 596,000 pregnancies that ended in 2002 through 2006. And the distribution of those pregnancies is about 75 percent live births, 12 percent spontaneous abortions, 9 percent elective abortions, and 4 percent other outcomes, which is

really similar to national survey data for pregnancy outcomes.

And then we selected a sample of 420 pregnancies and validated them through medical record review, and we confirmed 99 percent of our live births and 93 percent of our spontaneous abortions, 92 percent of our elective abortions, and 90 percent of other outcomes. Overall, the algorithm did a really good job of identifying these pregnancy outcomes. Next slide.

And we also did some validation work to look at the agreement in the dates. So for agreement on the pregnancy outcome date within 30 days, that agreement rate ranged from 70 percent for elective abortions, all the way up to 96 percent for live births. So it's really variable by the outcome type.

And when the gestational age was available in the medical record for review, the agreement within 30 days ranged from 70 percent for these other pregnancy outcomes to 98 percent for live births. Next slide.

So this slide is very busy, but I'll just quickly orient you to it. So this is showing the differences in gestational age from what the algorithm just set as the gestational age from what we found in the medical record review. So zero means that there was no difference between the two dates, from the manual review and the algorithm. So if you look in the upper left corner, those are for live births, and you can see that most of the algorithm gestational ages cluster within a week of the gestational age that was found in the medical record.

But if you move across to the upper right- hand corner, those are for spontaneous programs, and in the lower left-hand corner, for other pregnancy outcomes, and in the lower right-hand corner, for therapeutic abortions, you can see that there's a big spread in the difference between the gestational age the algorithm assigned and what we found when we went and did the medical record review.

So that's just something to keep in

mind, we're doing these studies that require really precise estimates of the timing between vaccine exposures and pregnancy outcomes. Next slide, please. Excuse me.

So we have used this VSD algorithm to create an annual pregnancy data file since 2010 in the VSD. We feel that this algorithm performs well for identifying pregnancy episodes and is currently being used in several of our ongoing vaccine safety studies. And we've made a few tweaks and adjustments to the algorithm program over time to improve its performance. Next slide, please. Sorry. I'm still suffering a little bit from this virus.

So one of our sites in particular has some issues with estimating gestational age, because most of their data came from claims data rather than from their own EMR system. So they developed and validated a refinement method for gestational age estimated, and that was based on CPT procedure codes for these routine prenatal tests. And I've written some of them before --

below, so -- some of these tests were in the electronic medical record or in the CPT procedure code data, it would kind of refine the gestational age estimate that was set by the algorithm. The next slide, please.

So this particular slide validated -- ran this refined gestational age algorithm and validated it with medical record review and looked at the birth certificate, and the dashed line there just represents, again, zero is the difference between what the algorithm says and what the birth certificate says. So the dashed line represents just using a fixed 280-day algorithm, and the solid line represents their CPT code refinement algorithm.

And you can see that they were able to improve the agreement and tighten up that agreement on specific dates by using this refined algorithm. And so we've incorporated that into our VSD work for this one particular slide. Next slide, please.

So after we figured out how to identify

pregnancy outcomes and dates, our next challenge was to link mothers to infants. And there are a lot of challenges to doing this. You know, most moms are going to be biologic moms, but we have women who are going to place their child for adoption or doing surrogate pregnancy, and when those women come into our system, we may have their prenatal care, but then we have nothing on their babies, obviously. They kind of disappear.

And sometimes babies can be lost because they go onto the father's insurance plan, or there's a delay getting them insured with us, so they don't appear on our record systems for a while. And, of course, lots of people these days have discrepant family names, so it's oftentimes not easy to link people up.

So each VSD site develops their own algorithms for linking mothers to infants, and most of these use some type of probabilistic matching, so looking at combinations of names and dates of birth and delivery dates and health plans, (inaudible), and the like.

And then we took -- and for most sites -- for -- most sites were able to link more than 90 percent of more of their birth record, and one site has 34 percent linkage within the VSD. Next slide, please.

So we validated a random sample of 50 of these linkages per site with medical record review, and the medical record abstractors were asked to look for evidence in the record, such as shared name, shared insurance plan, equivalent delivery dates, and dates of birth, and we are able to confirm 100 percent of our mother-baby links. Next slide.

So our other challenge was collecting important information on covariates, and so we created a new VSD dataset in 2013 to capture some of these important potential confounders. Some of the information we pull comes from medical records and some of our prenatal registries that exist. That's why -- and some of the information comes from birth certificates.

So we now have a pregnancy covariate

file that includes maternal height, pre-pregnancy weight, delivery weight, maternal education, marital status, parity, gravidity, tobacco and alcohol use during pregnancy.

And we also built a teratogenic medication file, so normally the VSD doesn't include any type of pharmacy data outside of the vaccines, but we do have the capability of bringing this pharmacy data in, and so we've built this one specific ancillary file for these pregnancy studies. Next slide, please.

So this summarizes the VSD studies that we've done to date, and some of these have been published, and some of these are under review, and some of these are just ongoing. And we've described vaccination rates during pregnancy. We've looked at preterm delivery and small for gestational age in relationship to seasonal influenza, pandemic H1N1, as well as the vaccine in Tdap.

We've looked for acute vaccine adverse events, the things that are common after

vaccination, like lymph swelling, allergic reactions, fevers, in pregnant women. We've looked at obstetric events, so looking at the risk of gestational diabetes or gestational hypertension and preeclampsia, eclampsia, Caesarean delivery, following the vaccination.

We have ongoing studies underway to look at birth defects with seasonal influenza and Tdap vaccinations. We're looking at inadvertent vaccination with HPV vaccine. And we've also done a study of spontaneous abortion and the seasonal influenza vaccination, and this was a case-control study, and I want to point out that for this particular study, we were not able to use the algorithm because it wasn't precise enough in getting to the timing of fetal demise and vaccination.

And this particular study required a lot of very in-depth chart review, and people were going out and reviewing the actual ultrasound reports to really hone in on the date of fetal demise. But it just kind of gives you an example

of the breadth of studies that we've done using these data, the algorithms in the VSD. Next slide.

DR. STAFFA: Dr. Naleway, I'll need to ask you to wrap up.

DR. NALEWAY: That's fine. I think I have two more slides. The VSD strengths, we have a large, geographically diverse cohort. We're able to identify other pregnancy outcomes in addition to live births. When we do need to go back to the chart to confirm events or correct additional covariate information, we have access to the EMR data. There's no selective recall of events or exposures. We can link mothers to infants, and most sites incorporate birth certificate data. Next slide.

And the limitations of the VSD is that we do miss pregnancies and prenatal care that occur outside of our system or occur like at home, for home births. The algorithm performance is really good for a live birth, but is not great for the non-live birth outcomes.

Coding changes and data availability at participating sites will impact the algorithm's performance. We have to estimate gestational age, or sometimes our gestational age is too imprecise for some of our studies. Medical record review is often required, and that's time-consuming and resource- intensive. And we have a delay in receiving birth certificate data from the State, which automatically limits the timeliness of the algorithm for doing prospective studies. Next slide.

So we're still doing a lot of work on this topic within the VSD, and we have some future directions and goals that we want to accomplish. We'd like to possibly refine the algorithm by including additional data from sites, so scaling back up to more of that Cadillac model that Hornbrook initially developed, with laboratory testing and ultrasound data. We'd like to possibly incorporate fetal death certificates. And we want to continue to analyze and refine our covariate data. And we also need to prepare for

the implementation of ICD-10 coding, which will have an impact on the algorithm.

And, finally, I just want to say that I do believe that the PRISM group within FDA is now going to work with our algorithm and see if they can use that for their studies.

And my final slide is just a thank you to all the people who've worked with me on the VSD Pregnancy Working Group. They're all listed here. Thanks for your attention. I'm so sorry for my quirky (ph) voice and my coughing.

DR. STAFFA: Thank you, Dr. Naleway, and hope you get a chance to rest your voice a little bit in anticipation of some questions. Our final presenter for this morning's session is going to be Dr. Adrian Dana, who's going to be talking to us about some strategies for using pharmacovigilance to look at exposures in pregnancy and outcomes.

DR. DANA: Good morning. Thank you so much for asking me to speak this morning. And I guess my first slide is also my disclaimer. I'm a

full-time employee at Merck, so -- but I wanted to -- first of all, I'd better figure out if I can work this. Okay.

What I wanted to do a little bit this morning was to talk to you about -- a little bit about the industry perspective on the pharmacovigilance and monitoring of pregnancy exposures. And so I wanted to talk a little bit about following adverse event reports and risk management planning, which I think we haven't talked to much about in this group as we look about licensing new products; a little bit about our post-marketing experience -- and I'm not -- I know we talked a lot about registries yesterday, but what I want to do is hit a few high points that maybe we didn't emphasize enough in our discussion up to this point; and then a little bit of future directions, which I will make the disclaimer now is largely my own opinions, but some things that I have concerns about or things that I think we need to think about. Oops.

So I'm not going to, again, dwell a lot

on this, because we know that the information on the use of drugs and vaccines is -- in pregnancy is especially important, and it's very important to make treatment decisions and for counseling of patients. And safety information is difficult to come by.

And I wanted to just dwell for one moment on that last bullet, because I didn't have a good way to put the shorthand in there, but we have medicines that are not indicated for use in pregnancy, meaning that there are medicines for which there's not a particular benefit to the pregnant woman. And so when we can, in an abundance of caution, we try to avoid those medications. And so for those drugs in particular -- and I work largely with vaccines -- so for those drugs, we just recommend avoiding it and deferring the vaccine until the pregnancy is over.

And so the only information that we often have on those kinds of products are inadvertent exposures. And so we need to collect all available information from those exposures,

because that information is vital to inform the use in human pregnancies. And I'm going to skip this slide, because we've talked about it.

So approaches to post-marketing surveillance in pregnancy, you know, one of the things we haven't talked as much about, but that we in industry do and is -- remains an important cornerstone is adverse event reporting and adverse event surveillance. And a systematic approach to data collection and analysis in this setting is critical.

Spontaneous adverse event reporting still remains particularly valuable for detection of rare -- especially rare and serious events. And while it -- adverse event -- spontaneous adverse event reporting may not be able to confirm a signal, it is still an important means of signal generation and signal detection.

When there is a report of an exposure during pregnancy, these reports are a reason for us to do some additional follow-up. And so we do make multiple attempts to try to find pregnancy

outcome information when one of these exposures is reported to us.

However, as I mentioned earlier in the meeting, there are times that privacy laws and regulations create a barrier for us for data collection in that once we receive a report, there are times when we are prevented by law and regulation from following up with that patient or provider. We do request that they remember to tell us what happened, but you can imagine that that isn't always very successful.

So approaches to post-marketing surveillance in pregnancy -- and, again, we've talked about it, and I'll talk a little bit in a minute about our experience in industry with pregnancy registries. And we've talked again about these large healthcare databases and claims databases and epidemiology studies.

One of the things I do want to emphasize and I think has been talked about by some of our previous discussants is that when we use these

large data systems, the ability to access the medical record is really key, and we found with some of our studies -- maybe not so much in our pregnancy-related studies, but in some of our other post-marketing surveillance studies, that if you have an outcome of particular interest or you need to -- you've generated a signal and now you need to confirm it, that you need to be able to get down to the level of the individual record in order to do that.

And we've seen that, for instance, some of our exposure data on the vaccine side is maybe not as accurate as we would hope from some of the claims databases. So it really is key to have the ability to drill down.

I wanted to just talk a little bit about our experience at Merck. We have operated pregnancy registries based on spontaneous exposure since the mid-'90s. We do capture information from inadvertent exposures, again, which may be our only source of information.

And I wanted to talk about our goals.

The goal -- the first one is sort of obvious, to detect important adverse events related to pregnancy exposures, including events in the exposed infants. But our other major goal, and maybe we haven't quite talked enough about this, is to provide healthcare providers and patients with information to help inform medical decisions. So we do have a goal stated in the registry to inform providers, and we do that, and I'll talk about how we do that in a moment, but we do that at regular intervals.

So the patient accrual in these registries is by voluntary, spontaneous reporting by providers or patients. And so because these drugs in general are not indicated in pregnancy, the exposures are inadvertent or off-label, and so enrollment prior to exposure is not really possible in this circumstance. And we do make an effort to inform patients and providers about the registry. Again, we talked about via websites and the product information and also that we present our data at scholarly functions. And, again, I'll

talk again about another means that we use when we talk about the report.

I wanted to mention a couple of things about our criteria for enrollment. Obviously there has to be an exposure during pregnancy. One of the important things, though, to realize is that that exposure window has to be defined for each product.

And why do I say that? Well, it's pretty obvious for a drug, but we have vaccines, and some of those vaccines are live virus vaccines or live organism vaccines. And so you may need to think about, for instance, your viral kinetics, how that virus works, and you may need to back up your exposure window, realizing that that virus is going to continue to replicate, and you may have an exposure later on.

So as we talk about standardizing definitions, I think we do need to think about the times when we need to be product-specific or situation-specific. We do need to have an identified healthcare provider, because we take

information -- we'll take information from any source, but we like to have a healthcare provided identified so that we can get as much accurate information as possible. We need to have a unique patient identifier of some kind so that we can match the data up. And we have to have it -- the enrollee has to be in a country where the registry's active.

There we go. The data, again, I'm not going to spend a lot of time on this. We talked about prospective and retrospective reports and that the prospective reports are those received before the outcome of the pregnancy is known and that prospective reports are the primary analysis cohort. We do use external expert consultants to review our data on a routine basis and for every one of our annual reports.

I wanted to spend a minute on the cumulative reports. We do do periodic, which in our case is usually annual, cumulative reports. And what do these reports include? Well, they do include the data that we have to date on our

primary analysis cohort and the rates of the -- of outcomes of interest, which are usually the standard, you know, pregnancy outcomes, teratogenicity, and if we have specific outcomes that we are looking at -- so, for instance, for our Varivax registry, we were looking for anything that might look like congenital varicella.

And -- but we also include the -- what we know about any abnormal teratogenic or abnormal birth outcomes that we are aware of from the rest of our data. So we look at the pregnancy registry. We look at the enrolled, and we report on the enrolled. We report on retrospective cases that came out of the registry. We also report on those abnormal infant outcomes that are from non-registry countries, that are from sort of whatever we have in our database.

So we can't -- because we have no denominator, we can't really look at rates of spontaneous abortion, for instance. But because of the -- of any birth defects, that might -- that information might be important and might be of use

in counseling women. We include sort of the universe of data that we have in our database. And we distribute that annual report to regulators, obviously, to health authorities, to medical societies that would be interested, and to any providers reporting to the registry.

So if someone calls in to report that they've had an exposure, we will, at that time, give the most recent report to the healthcare provider so that that can form the basis of counseling that patient. And then the next year, we will automatically send the updated report to that reporting provider.

So I wanted to spend a minute on risk management planning. Risk management is a discipline that acknowledges that risk is inherent in medicines. Risk management planning involves risk assessment and then risk minimization. It is proactive. It is a proactive approach that is required to minimize potential risks.

Formal risk management plans are prepared for any new product submissions and with

certain other significant submissions. This is a formal document which summarizes the risk information that's known to date and plans to manage those risks, and it also plans to refine the risk profile going forward as new information is gleaned.

The RMP, risk management plan, summarizes the safety and risk data for the product and outlines safety-related actions to address them. Pregnancy exposures are routinely considered as part of our risk management planning.

In many plans, it is commonly considered missing information because studies are not available. But if the product has a potential for significant use in women of childbearing age, or if there was a potential safety concern, then a plan for monitoring post-licensure should be concluded formally as part of the plan. Pregnancy questions should be addressed systematically and may require multiple data sources and methodologies. I'm sorry. I don't seem to be

able to work this slide thing.

So I wanted to give you an example of risk management planning that we've done for one of our products, and we did have, you know, sort of a multi- arm approach to following the pregnancy exposures. So obviously we used our routine pharmacovigilance efforts, and as I mentioned, we have an intensified effort to obtain safety information, including outcomes.

We also arranged to obtain information from the Swedish Medical Birth Register for this particular product. Since the time that this was developed, that has become less of an option because we've had trouble getting that data, but at the time, we did get that data for several years.

We set up a pregnancy registry. We also had a post-marketing safety surveillance study, and as a part of that study, we did use the descriptive epidemiology of exposures during pregnancy that happened during the course of that study.

We also arranged to do some Nordic registry studies where we took advantage of the fact that in some of the Nordic countries, there are really very complete vaccine registries as well as pregnancy outcome registries and tried to marry that data to see if there were any abnormal outcomes that we could detect.

And, of course, we used the product labeling to inform that the product was not really intended for use during pregnancy and to impart some information on pregnancy registry and how to report to the pregnancy registry.

So future directions, where are we going? Well, I think that the use of electronic medical records may change post-marketing product safety monitoring significantly. And, again, this is my opinion, but I really suspect that regulators are going to try to capture complete information by linking directly into some of these electronic medical records. And I think that that's a -- that's probably a good idea and a good way to capture post-marketing safety events.

I think it -- my fear from the manufacturer's side is that we will get fewer reports ourselves, and so that our monitoring, which we must do, both from a regulatory perspective and from an ethical perspective, will become more difficult if we are not able to access the data. And so I would raise this concern with the FDA, that, you know, we have an obligation, and we take it very seriously, to monitor the safety of our products, and we can only do that if we have a way to share that information.

I think a global view and global collaborations are needed, and we do need to address somehow the privacy laws and regulations that make data collection and follow-up difficult for manufacturers. I think it's very interesting. You know, there's a transparency movement, and the data is now becoming available on every website, and yet for the purposes of product safety, I have trouble following up sometimes and getting data to help protect patients' interests.

Pregnancy outcomes may have differing

influences in different regions, both by, you know, customs and medical treatments, et cetera, and so that needs to be taken into account. And cooperation and collaboration is obviously essential.

I think there is a need to share best practices, and I think a meeting like this is really wonderful, and we need to continue to share those best practices among all the stakeholders. And there does need to be a development of certain accepted standards and definitions. And I would say, you know, certainly in the vaccine world, we have an example of the Brighton Collaboration as something that has both industry, regulatory, academic representation to develop case definitions, and maybe some -- that could be a model in future directions.

So in summary, information on the safety of medicines in pregnancy is critical, but difficult to obtain. In many cases, post-marketing data is the only data available. A systematic approach to collection and analysis of

post-marketing data still remains important. The possibility of risk -- of pregnancy exposure should be considered routinely as part of risk management planning. And proactive risk management planning should be developed as appropriate. And cooperation and collaboration among the stakeholders is key.

DR. STAFFA: Thank you, Dr. Dana. And, again, I'm going to invoke the Chair's prerogative again, so hang on to your questions. We will do clarifying questions, but we're going to postpone that and roll that into our discussion. In the interest of trying to respect the folks who signed up for the open public part of the meeting -- and we're only just ten minutes shy of starting that -- I'm going to go ahead and proceed with that part, and then we will revisit clarifying questions at the beginning of our discussion session. So at this point, I will turn it over to Dr. Gelperin, who will be coordinating that part of the meeting.

DR. GELPERIN: Thanks, Judy. We will

now begin the open public comment section. Both the Food and Drug Administration and the public believe in a transparent process for information-gathering and decision-making. The comments provided may be considered for discussion by the panel during the panel discussion session.

Speakers are asked to step up to the podium at their assigned time and to speak only when recognized by the moderator. Speakers have been allotted five minutes, and we will use a timer to keep track of the time. We will turn the timer on when you begin speaking. A yellow light will come on when you have one minute left, signaling you to wrap up. The red light means to stop speaking and return to your seat.

Will Speaker Number 1 please step up to the podium and introduce yourself? Please state your name and any organization you are representing for the record.

DR. CONSTANTINE: Good morning. My name is Maged Constantine. I'm an obstetrician maternal-fetal medicine at the University of Texas

Medical Branch in Galveston, and I'm representing the Society of Maternal-Fetal Medicine. I have no conflict of interests.

As you all know, the medication use in pregnancy has been steadily increasing, and the average number of prescriptions or medication used in the first trimester is more than two, the last time I checked, which is important, especially in the first trimester, because it's a critical period for organogenesis and a time when many women are unaware of their pregnancy.

Add to this that the majority of drug trials exclude pregnant women and the vast majority of therapeutics and vaccines were never studied during pregnancy during the initial research and development, but the data we have on them are mostly from late- stage retrospective studies and post-marketing registries.

Teratogenicity, although it's important, however, is not the only safety concern. Other concerns of pregnancy especially include dosing. There's lack of data on dosage for a lot of

medication in pregnancy, and typically physicians extrapolate drug dosage regimen from non-pregnant subjects or even men, which can lead to over- or under-dosing and potentially fetal toxicities. And this is due to many factors, and particularly the lack of pharmacokinetic trials in pregnancy.

This graph show the percentage of PK trials in pregnancy, which is less than 2 percent of all PK trials in general. And this is important because of the changes in pregnancy which impact drug disposition and transformation as well as the sex differences between men and women, which weren't initially addressed. Recently, there's a push to actually start doing more cell and animal studies, both in male and females.

Thus, the need for drug research in pregnancy and lactation. I'll just give you some brief examples how this may have potential benefits. Start with magnesium sulfate, which is a commonly used medication in pregnancy to stop either preterm labor or prevent seizure in woman

with high blood pressure or to protect fetal brain in infant born prematurely. However, the dosing regimen is varied, there's no therapeutic level, and the duration is usually initially a few days; however, a lot of physician used it for prolonged period of time. And that wasn't initially thought to be important; however, there are a lot of studies that show that prolonged dose of magnesium may lead to fetal bone loss and fetal fractures, which led the FDA recently to change the classification of magnesium to a Category D drug. And this thing would not have been picked in a registry.

I'll give another example on hepatitis C. There's a lot of newer drugs that actually came to the market for hepatitis C and promised cure for hepatitis C; however, in pregnancy, we don't treat hepatitis C because we don't have medication to treat hepatitis C, and still the rate of transmission's around 5 percent, and that's something that's never been addressed, and the registry probably will not pick it up.

I can give you a lot of other example, but this is some of them. For example, the newer oral anticoagulants; some antiepileptic medications; SSRI; contrast agents, especially for the MRI; statins; and other medications.

Not just the short-term effect of this drug and safety; however, the long-term effect of this drug. This is a paper that was just recently published in JAMA that link acetaminophen usage in pregnancy to hyperkinetic (ph) and ADHD in neonates. And this is something -- it's very important, and actually was brought up yesterday by Lisa (ph), who mentioned about the long-term neurodevelopmental outcome of infants, and that's something that usually is not picked up by registries.

So, again, teratogenicity, while important, is not the only safety concern. And the suggestion that we have, that future registries should address other important safety variables, especially dosing. Ultimately (ph) can design registries for opportunistic medication,

the medications that are used infrequently in pregnancy, include medications that are currently in use and medications that are newly approved for other indications as well as provide long-term neonatal follow-up.

Other suggestion may include putting alerts in patients' electronic medical record to notify patients (inaudible) registries as well as linking users or try to attempt link the users of drugs in pregnancy to child medical record.

And, lastly, incentivize pharmacokinetic and vaccine studies in pregnancy and lactation. At the end, I would like to thank you for the opportunity to present on behalf of Society for Maternal-Fetal Medicine. Thank you.

DR. GELPERIN: Thank you. Will Speaker Number 2 please step up to the podium and introduce yourself?

DR. DEWULF: Good morning. My name is Lode Dewulf, and I'm here all the way from Brussels on what is a national holiday because I'm very passionate about together closing this gap in

public health, which is a huge and global issue. I work for UCB as their Chief Global Patient Affairs Officer, but the following comments are really my own.

For starting, I would like to thank Dr. Nguyen and Dr. Greene, who is no longer with us, for their comments this morning, which I found very inspiring, but also a little bit at odds with my feeling as I left Day 1 yesterday.

One of the statement that was said was, "Press us, and help us." And I'd like to start my first slide with a quote that I got from a dear friend, who's on the phone and listening in, Christina Bucci-Rechtweg from Novartis, which is a -- sorry, it's a non-U.S. quote, but I think it still works.

I think what brings this group together is that all of you have been pioneers in doing exactly this. You've gone where others have not gone. I do think it's time to raise the bar, and I'd like to stimulate that discussion with ten questions that I have for myself and for you.

Twenty seconds each, so it should keep me in time.

The Number 1 is (inaudible) where's the patient? If I look at the panel, if I look at the discussions, there was, what -- Julia (ph) was the only one really talking from that side. If we can't get the patients into this room and into this discussion, what makes us believe we can get them into our studies?

There's also a very famous Belgium artists which is coming on a U.S. tour very soon called Stromae, and one of his songs is "Papaoutai," which means, "Daddy, where are you?" And as a man, I think somebody should make the point that there's also a man -- a male aspect to this whole debate, where we have spent 95 percent talking about women, even though our contribution is admittedly much smaller.

Okay. So and then there's a last thing -- there are -- and this is a number I got at a previous meeting -- 250,000 women in the U.S. alone using about 1,000 different medical apps (ph) to self-register their pregnancy, and that

has not been mentioned once as a data source.

So we have to move from how do we get patients in the study, which was the most frequently asked question during this meeting so far, to how do we bring the study to the patients, totally turning around the way we think. And I'm actually using an Eli Lilly slide, because I think they deserve credit for really leading a lot of us in how we approach patients no longer as data sources, but as valued collaborators in our research efforts.

My second question is what are we really communicating? I think in this room, it's fine, but we have to be very careful. I really agree with the dysmorphologist to exclude Down's, but I don't know why I have to explain to a mother with a Down's kid that we don't consider Down's a congenital malformation or abnormality. It just doesn't make sense. So we have to be very careful. If we say it's only 2 percent and exclude something as important as Down -- I don't know any such mother who doesn't consider --

that's a very important life event for her, her family, and her kid.

We also keep referring to pregnancy as a disease because we call them patients. I think that's not the right term. We call it a risk and an adverse event. I think that's -- be very careful how we communicate that.

The third question is what risks really matter to patients and are understood by them? Okay? Because that's very important, comes back to the Down's example. The biggest fear that we found from doing an Internet search on hundreds of thousands of English-speaking blogs around pregnancy is the biggest fear is the inconsistent advice received from different healthcare professionals. So if all we do is just align our debate and our message, that would be very important.

Okay. My next question, what about benefits? That's probably also been under-represented here. There is a reason why the control group is not on the drug. Maybe their

disease, as Dr. Clowse said, is not as bad, and that may also independently contribute differences you see. Okay?

And then, of course, we already know that one in four patients is already entering pregnancy with a pre-diagnosed medical chronic condition like diabetes, major depressive disorder, or hypertension. And so that will only increase. So those are benefits that we can't ignore if you'd continue to treat those diseases.

And last, but not least, how clean is our control group when 90 percent of the pregnant population is actually taking drugs? How will you be controlling for that? There may be other confounding factors. If we only look in one drug, we will not see that.

And this is a list just from the CDC, which they published recently. If you look at the 12 most -- or 11 most used drugs -- and none of them actually are what I would call new drugs for which pharma is still investing a lot of money, but these are the drugs that should concern us

from a public health perspective. And I think there's a lot of data on them as co-medication (ph) in existing studies that we're not harvesting.

Which brings me to Number 5, which is what can we do more with the existing data? Everybody says we need more data. I personally believe we actually have a lot more data than we're using. We have incredible databases that exists in Walmarts and CVS and Walgreens and the food industry, fitness, and there's a lot of health-relevant information in there. Nobody in this room is representing these people, and they have all these data about us. They know more about us and our family when we walk into their store than we think, and we have many recent examples for this --

DR. GELPERIN: Dr. Dewulf, one minute, please.

DR. DEWULF: Thank you. Number 6, what can we learn from looking beyond the U.S.? Two examples, there's now a quality label sponsored by

the UK Government for English-speaking websites with medical and health information that is an incredibly powerful way of helping the public. Another one, just across the border in the north, Motherisk in Toronto has been, for 30 years, serving exactly this population, has a lot of competence to share.

Clinical trials should not be ignored. There are more patients in clinical trials after registration than before (inaudible) we continue to kick out women and lose 50 percent to follow-up, we'll never have better-documented cases on pregnancy. Let's do something in that field as well. What drives the healthcare professional? We have to address litigation. Can we create a Phase II like safe harbor (ph)? That may change things.

In 2000, the patient got more information- empowered than the healthcare professional. What we're hearing today is that databases will have more information than the originator of the molecule, like Dr. Dana said, or

the regulators. Are we ready to deal with that? Because that's going to be the case. We won't have the data, and still we're going to have to set guidelines.

And last, but not least, my most important question, a little bit like what Sandy said, is I don't know what to tell my teenaged kids if I retire and if we haven't solved this issue.

DR. GELPERIN: Thank you, Dr. Dewulf.

DR. DEWULF: I think we need to work together. Thank you very much.

DR. GELPERIN: Thank you. Will Speaker Number 3 please step up to the podium and introduce yourself?

DR. EPHROSS: Hi. I'm Sara Ephross, a PhD- trained reproductive pharmacoepidemiologist. I have more than 19 years of experience in pregnancy epidemiology at GlaxoSmithKline and its legacy companies, and now I have to say starting with Burroughs Wellcome.

The chapter on pregnancy registries in

the recently published third edition of the AHRQ Registry User Guide states that "Well-designed and executed pregnancy registries are an efficient initial approach to assess the safety of biopharmaceuticals during pregnancy."

As we've heard over the last day and a half, pregnancy registries specifically designed per product remain an important tool. However, the traditional pregnancy registry is not appropriate for every medication, and the majority of medications do not have one. From my perspective, four challenges remain. We have yet to find economies of scales for registry awareness among healthcare professionals, follow-up of enrolled women, efficient use of scientific advisory committees, and effective linkages to other systems.

An example of an inefficiency in the infrastructure that we've heard a lot about over the last day and a half includes multiple registries for similar biopharmaceutical products and disease states.

Second, there's often limited capability to accurately project registry enrollment, which can result in unknown representativeness of the target population of exposed pregnant women. Dr. Holmes said it very well when he said, "Often our registries are not a random sample of society."

Third, other systems besides traditional pregnancy registries should be considered qualified to meet FDA and other regulatory post-marketing commitments. And, finally, we should consider ways to link better pregnancy registries and other primary surveillance studies to other exposure and outcome systems, many of which we've heard about today. This will maximize both the value of pregnancy registries and the value of these other surveillance systems and better enable us to design follow-up studies as appropriate once we have results or interim results from pregnancy registries. Thank you.

DR. GELPERIN: Thank you. Will Speaker Number 4 please step up to the podium and introduce yourself?

DR. DAVIS: Hi, I'm Bob Davis. I'm Governor's Chair at the University of Tennessee Health Sciences Center. I thought I would just take the opportunity -- and I thank you for the opportunity to give you my thoughts about what could be or what I believe is shaping up to be a comprehensive approach to patient pregnancy medication safety research and sort of taking the opportunity to give you my thoughts from 30,000 feet. Next slide, please. Or do I advance it this way?

So my thoughts today are really based on 20 years of experience and observations working in vaccine safety, with the Vaccine Safety Datalink at CDC and then in drug safety with the Sentinel Initiative led by the FDA. Many of the challenges that we're facing now are exactly the same, remarkably similar, overlap with the challenges that were faced by vaccine safety questions and drug safety questions.

What I see here today is really a critical mass of many different ways of

approaching this problem that I think can come together to provide a really wonderful infrastructure for United States' efforts in this direction.

In that sort of light, I want to just point out what is probably obvious to everybody here, but is worth repeating, which is that the large database studies that we've seen from, say, pregnancy registries, MEPREP, DoD, VSD, and then case-control studies that we've seen from Harvard and Boston University, are complementary and synergistic. They provide critical public health capability for both ongoing surveillance and deep-dive studies.

And that's, in fact, the approach we've taken in VSD and in Sentinel Initiative. We don't do one, and we don't do the other. We do them both. There are different people who are good in one, different people who are good in others. There's a tremendous amount of methodology development that is ongoing, that's interactive, and there's constant communication between the

groups that are doing surveillance and the deep-dive studies.

You know, I say this -- let me tell you why I'm making a big deal about that. I'm saying this because I feel like over the last day and a half, I feel like there's been a lot of jockeying for position because of limited public health funding, and that's understandable, but, frankly, I think that -- I think FDA, frankly, could play a very good role in creating an umbrella that brings us all together and helps us all work together and provides an overview and a framework so that we have a joint mission to collaborate for this purpose.

Some of the -- a point that was made previously, but, again, is worth going over is that at least one benefit that large database studies have is expanding the subject matter past just congenital anomalies, and we've been involved in studies -- I've looked at SSRIs that identified neonatal withdrawal syndrome, beta blocker usage associated with neonatal hypoglycemia, calcium

channel blocker usage associated with neonatal seizures.

Based on our findings here, we decided to do a large longitudinal follow-up study of asthma medication used during pregnancy in fetal infant growth. It was interesting and exciting to hear about VAMPSS' interest in this subject matter as well, again, I think pointing out really the strength that FDA could bring to this table to provide some overall direction and collaborative efforts in these regards, because I think that almost certainly those are complementary approaches that VAMPSS and MEPREP could be addressing this question with.

There are many future opportunities. I want to point out two, one that's one the slide and one that I forgot to put on the slide; just remembered it as I was walking to the podium. One is that EMR data is increasingly becoming available. It's extremely granular; can get things like blood pressure data on every visit that a woman makes during pregnancy at multiple

time points. And we have very granular tracking medication use. And I think it's sort of obvious that this allows for better studies of safety and also of comparative effectiveness of treatments, and, frankly, also patient-centered outcomes. I think some of these medications have different impacts on how women feel during pregnancy. And so I think that that could be in our purview as well.

The one thing I didn't mention is that we've done some work now -- Craig Hansen and I did some work in linking fathers of medication use prior to pregnancy. And so we are now situated to be able to look at epigenetic and transgenerational phenomenon and the impact of medications on the developing infant and fetus.

So just, again, to reiterate, I believe that what we've seen over the last two days is that we have a very complementary and potentially highly synergistic capabilities among the people and the researchers in this room, and I encourage the FDA to use their bully pulpit to really move

this issue or move this field forward and provide the capability and the umbrella infrastructure for ongoing surveillance in deep-dive studies. Thank you.

DR. GELPERIN: Thank you, Dr. Davis. Will Speaker Number 5 please step up to the podium and introduce yourself?

MS. CANTRELL: Good morning. I'm Susan Cantrell. I'm Vice President and Managing Director of DIA Americas, and I'm pleased to be here today and bring you comments on behalf of DIA. DIA, or the Drug Information Association, was founded in 1964 as a global professional society, neutral organization of individuals involved in discovery, development, and life cycle management of drugs, biologics, and medical products.

Our members comprise industry professionals, regulatory authorities, members of the academic community, and also patient advocates who work together to support the mission of bringing medical innovation to patients to improve

health and well- being worldwide.

And I bring you comments today just to highlight some of the work that we've done in this area in hopes that it might inform the efforts taking place here today and going forward. Our founding of the organization, in fact, was, in some ways, rooted in this issue. We were founded in 1964 as a result of the Kefauver-Harris Amendments to the Food, Drug, and Cosmetic Act that were related directly to the thalidomide tragedy of 1962, and so we've long made it a priority for the organization.

We held conferences on the topic of pregnancy registries in 2004 and 2006, and more recently, in 2012, we began an initiative related specifically to improving opportunities to develop data and inform medication use in pregnancy. We, in the last year, have held three multi-stakeholder discussion forums on this issue at our European meeting in 2013 and in 2014 in Vienna, and then last year at our annual meeting in Boston.

And we've had global participation from industry professionals, regulators, patients, and researchers to discuss this important issue, and the result of it has been three papers published in our journal, Therapeutic Innovation & Regulatory Science, and we've posted information on these papers to the docket in case you'd like to review the content of these.

They relate specifically -- the first of which was authored by Dr. Lode Dewulf, who we heard from a few minutes ago, and it's on the topic of a coalition effort -- a proposed coalition effort to address this issue in its totality; not just the collection of data, but the dissemination and use of the data as well.

The second paper speaks specifically to data collection methods, including a number of the issues that we talked about yesterday related to registries, and it talks about strengths and limitations as well as potential other alternative sources of data collection.

And, finally, the third paper, which was

published most recently, in March, proposes a framework, a multi-stakeholder framework that might be used to move this issue forward. And one item that has been clear from our work on the issue is not only is data collection critical to this, but communication and education are critical as well. So we need to create together a framework for sharing this information, both through regulatory channels as well as through healthcare provider channels and others, in order that the patients and the healthcare professionals have the information they need to inform medication use in pregnancy.

So, again, I offer you comments today on behalf of DIA just to bring this work forward to your attention in case you're unaware of it, in hopes that it might assist in our collective efforts and also to offer our support going forward. Thank you.

DR. GELPERIN: Thank you. Will Speaker Number 6 please step up to the podium and introduce yourself?

DR. ALLEN: Good morning. I'm AJ Allen. I'm a Senior Medical Fellow in Pediatric Capabilities and Bioethics at Eli Lilly, and I'm presenting some comments on behalf of Lilly. I should note these slides were developed by a group of us over the past few weeks. We use the term "alternative approaches" here, but I think probably "complementary approaches" is more appropriate.

The first thing that we think needs to be kept in mind is critical to this process of looking at whether you're doing a pregnancy registry or other types of research is what is the question that you're asking? In particular, one of the things that we think needs to be factored into this discussion, the discussion today has mostly been about risk, how do we assess risk? Same with yesterday. But we do think that we need to start thinking more in terms of what's the benefit risk?

That's actually, I think, the language that is in the new labeling, is you're supposed to

assess benefit risk before using meds during pregnancy. And, in fact, nobody uses a med because it has low risk. You use it because it benefits in some way. So that needs to be part of the discussion.

The other thing is that with these research questions, it's important to think about having a timely response as part of the answer. The next question that we think needs -- is critical to look at is what is the comparison group that's most appropriate and also what is the most appropriate methodology? I think the point here is that there's no magic bullet. The choice needs to be driven by the research question and on a case-by-case basis.

In terms of the study design, I think it's worth noting that most of the discussion has been about leaving patients out of randomized controlled trials or drug -- studies during drug development. I think we need to at least be open to the possibility that in some circumstances, it may be appropriate to look at alternatives to just

simply excluding women of childbearing age from trials and to consider is there a role for randomized controlled trials in this process?

And that needs to be done on a case-by-case basis, but obviously we're hearing that there's a great need there and that, really, you're not going to start getting at that benefit until you perhaps include women in these trials that are of childbearing potential and follow those that do become pregnant.

Looking at other methods, the case-control -- we've noted with the OTIS VAMPSS study, you've got complementary approach with case-control and cohort. The two of them work together, again, looking at what's the most appropriate methodology for the relevant question?

And in terms of the data sources that are being used in the study, it's worth looking at a variety of data sources and exploring new ones that we might be able to generate. For example, patient- reported outcomes through social media applications or mobile applications is something

that has been mentioned a number of times, but are there ways that we could systematically incorporate this into existing research or perhaps capture some of that data in some of the systems that are out there that are being developed?

One of the persistent problems with many of these datasets is the issue of missing non-life (sic) birth outcomes, and are there ways that we can start to get at that better? And as was noted during a couple of presentations, mother-baby linkage is often a challenge that's a question, as is the exposure of pregnancy in time. So, again, we need to be flexibility and look at what's the most appropriate data source for the project being considered and the question.

Some other considerations, we have here patient input may be important in the design of a pregnancy program. I think we would say that in the vast majority of cases, you want to have that. There may be some cases where it's not as -- may not be as useful; for example, in claims database studies where you're really not interacting

directly with patients. But in as many cases as possible, it seems like it's important to try and get that input.

Standards for data capture are also a critical need. It would be wonderful to be able to compare the data across multiple sources and do that more easily, and that's something that, right now, we can't easily do.

So in closing, I think it's important that this be a collaborative effort between industry, academics, FDA, and other regulatory agencies. Current methods are necessary, but not sufficient. We need some new thinking, and we should be open to the possibility in the future of randomized controlled trials playing a role. Thank you.

DR. GELPERIN: Thank you. Will Speaker Number 7 please step up to the podium and introduce yourself?

DR. DUBLIN: Good morning. I'm Sascha Dublin. I'm a scientist at Group Health Research Institute, and I'm also a clinician at Group

Health, where I see patients one day a week. So I'm very involved in using our EMR as an end user. Group Health also has a pretty substantial research program using the EMR, and I've had research experience as part of the Sentinel Initiative and also MEPREP, and it's those experiences that inform what I'd like to share to you today, about my excitement about the potential for greater use of EMRs to study medication safety in pregnancy.

So I'm just going to briefly orient you to Group Health Cooperative as sort of an example of a setting where I think there are really rich data that, if we can just learn to harness them better, could be very useful for answering the questions we care about. So Group Health is a medium-sized HMO, about 650,000 members. We have our own delivery system, with 25 clinics where about 400,000 of our members get all or nearly all of their care. And this means that because we're their provider, we have very deep and rich clinical information captured in the EMR for those

patients. We have other members who see contracted providers, for whom we have claims level of data, but not the same richness in terms of lab data or vital signs and clinical notes.

Things that make this kind of setting useful for research is that we have a defined and accessible population, so we have a pretty good denominator, and then we also have high-quality and clinically relevant data that we have invested over the past years to organize them for research use. And I think that there are many sites like us that have made this investment already. There are also many potential sites out there that, with some infrastructure investment, could be brought up to that same level of organizing their data in a way that it's accessible for research use. And I'd like kind of point out in response to a speaker's -- one of the panelist's comments earlier said in many cases, these data can stay behind the firewall, and then we can use things like query tools and distributed approaches to access them while the organization retains control

over its own data, which helps a lot with concerns about patient privacy. Sorry. I'm having trouble with the slides.

So I won't go over all of these, but I just wanted to show you some of the things that facilitate researcher surveillance in this setting. On the left, the kinds of automated data files we've been able to develop include things like both ambulatory and inpatient care encounters with diagnosis information; the pharmacy dispensings; radiology, laboratory, pathology reports, we can access these and have -- Group Health developed an ongoing body of work with natural language processing to extract concepts, particularly from the pathology and the radiology reports.

On the right, institutions like Group Health marry a research competent with a healthcare delivery organization. We also have things like survey research programs. We can call people and conduct interviews and gather data through in-person communication. And so we have

those capabilities. And, again, I think there are many organizations out there that have both these data and the ability, then, to contact and recruit patients into case-control studies or other kinds of data collection.

So things that the EMR can do -- and some of these, we've been exploring at Group Health already, and many of our sister organizations in the HMO Research Network have been doing this. We've talked quite a bit yesterday about how could we harness the EMR to help with recruitment into registries, to alert patients and providers when there are opportunities? Certainly we can use best practice alerts when a program woman is seen, and the EMR can tell if she's program, and it can tell if she's on a medication.

I think it's important that we consider the real-world workflow. So so much of this work at Group Health in my practice and our clinics is actually not done by the MD anymore. My medical assistant and my LPN sets me up for success by

entering orders and pending them, populating the patient's after-visit summary. Those are people we need to think about as we develop tools. We can do secure messaging to providers and even direct to patients. We can push out questionnaires.

Things that physicians like Mike Greene are -- and as you showed us, the way that you enter the data into your structured OB intake form, those data live in the EMR in a structured way and can be harnessed. We can pull those back out. Some of the Kaisers are doing routine prenatal depression screening, with a PHQ-9 depression tool.

We can pull out those structured data as well. So if you put it in a structured form, we can get it back out, and that can become a tool for research, and then the rising value of natural language processing, to let us harness the material that's in that (inaudible).

So we've obtained and catalogued our clinical notes. I can search for the term "e-

cigarettes" and find all the notes that it's occurred in in the last year, two years, five years. So these are tools that we should be thinking about how to harness to really get into the EMR and use those rich clinical data.

So I think I'm out of time for my brief example. I think my take-home message was just that while randomized trials have studied a total of 3,000 women with mild to moderate hypertension in pregnancy, we could create a cohort now of 29,000 women at three health plans with rich blood pressure data and medication data. And I think these opportunities really are out there to be explored, and there's huge potential here.

DR. GELPERIN: Thank you, Dr. Dublin. Will Speaker Number 8 please step up to the podium and introduce yourself?

DR. SUMMARITANO: Thank you for the opportunity to speak. My name is Lisa Summaritano. I'm a rheumatologist at the Hospital for Special Surgery, Weill Cornell Medical Center in New York. But I'm here today as a

representative of the American College of Rheumatology to express our support for the FDA effort in promoting more rigorous standards for pregnancy registries and to hopefully work with you to ensure greater participation by both physicians and patients.

In January of this year, the ACR hosted a Representative Health Summit in Washington, D.C. on the management of fertility, pregnancy, and lactation for women with autoimmune diseases. We brought together specialists in rheumatology, gastroenterology, OB/GYN, other fields, researchers in pregnancy, neonatal medicine, and teratology, as well as members of patient advocacy groups and regulatory agencies, including the FDA. Our goals were to review available data on management of autoimmune disease patients in pregnancy and lactation, to better understand ongoing regulatory efforts concerning medication use in pregnancy and lactation, and to define future research needs in this area.

As rheumatologists, we realize that it's

the medical specialist who starts the disease-specific medications that may ultimately raise concerns during pregnancy. And we feel it's the medical specialist who's best equipped to weigh the risk of treatment for the mother versus the risk of no treatment, which is often active, uncontrolled disease. The risk of active disease is often greater for both mother and fetus than the risk of the medication.

We strongly suggest approaching the professional societies of rheumatology, gastroenterology, and others to form working groups to partner with the FDA and to use these organizations' websites and professional meetings to educate physicians, increase awareness, and ultimately increase participation.

We also suggest that disease-specific registries be supported to permit appropriate disease- matched controls and the evaluation of pregnancy outcomes beyond congenital malformations, such as preterm birth and growth restriction.

Finally, given the tremendous efforts described here, to establish the infrastructure for pregnancy registries as well as the effort towards increasing patient recruitment, we suggest considering additional collection of data on lactation during the first postpartum year while following up the neonate.

We have very little information on safety of most of our drugs for lactation, often forcing our patients to choose between breastfeeding and effective control of their disease. It shouldn't be this way. Thank you.

DR. GELPERIN: Thank you. The open public session portion of this meeting has now concluded. Thank you for your participation.

DR. STAFFA: Thank you, Dr. Gelperin, and thank you to those who took the time to come and speak to us today. At this point, I'm going to allow a few minutes at the beginning of our discussion, which is a bit shortened -- do people have burning questions for anyone who's presented this morning; any of our speakers, any of the

folks who came to the open public hearing portion? Again, I'm going to ask for burning questions, burning clarifying questions only, because I want to reserve time to launch into more of the discussion part. But does anybody have anything they really feel they need to clarify before we can have a good discussion? Dr. Greene?

DR. GREENE: I'm not sure if it's burning, but it's at least smoldering. I had a question for Dr. Hansen. In your presentation, you mentioned that a baby had to be continuously enrolled for 30 days after birth to be entered into your database, as I understood it, and I wondered if baby, theoretically, let's say, was born within anencephaly and died within a couple of days of birth and wasn't continuously enrolled for 30 days, if that would be missed in your surveillance.

DR. HANSEN: This is Craig Hansen. Thank you for that question. Actually, I said that slightly incorrectly. It was 30 days, or up until the day of birth. Sorry about that.

DR. STAFFA: Dr. Cragan?

DR. CRAGAN: This is Jan Cragan. Peggy Honein sent me a message and wanted me to ask if anyone had information or perhaps just an impression of the cost of some of these alternative approaches. So how much does it -- would it cost to maintain MEPREP versus VAMPSS versus some of the disease-based registries, like the OTIS registries or the North American AED. And I don't know that there's real -- people have compared that, but we wanted to see if anybody has any comments.

DR. CHAMBERS: I could -- this is Tina Chambers. I could say that there's certainly an economy of scale so that the larger number of products that are under study from our perspective -- and I think I can say this for VAMPSS as well -- that there's a dramatic economy of scale as more products come under study, and I'm sure that's true with the alternative approaches, where, you know, you're able to ask multiple questions within the same dataset. That being said, I don't know

how to put a price tag on that, but it is an interesting question.

DR. STAFFA: Susan, do you have any comments on that?

DR. ANDRADE: I don't know the budget, and we have people who do (inaudible).

DR. STAFFA: Trinka, comments on that from DoD perspective? You're going to have to turn the mic on.

DR. COSTER: You know, to maintain a full database and all the contractors and cleaning up of your data and pulling it in, and so costing, probably, about $700,000. You know, so then -- and that's with built algorithms for drug utilization, risk outcomes, and -- that are also maintained.

So basically -- and we're updating not just mother-child. We're updating our nine million beneficiaries for drugs, so we never really cost the difference between doing it just for mother-child, but that's really for all drugs, really, vaccines, any product, for the use of that

product, to do algorithmic approaches, maintaining a sandbox that you could use SAS datasets and link to your production system.

So it's hard to really -- you know, to cost it out, but it ends up being -- because you want clean data, you want everything to be -- and certain algorithms to be validated against it, it ends up costing a bit for -- and new data elements added means new SQL -- you know, new codes getting developed, so I'd say that's about the average cost.

DR. STAFFA: Dr. Mitchell?

DR. MITCHELL: Yeah, and I would just modify Peggy's question; compared to what? And I think that -- pardon?

DR. CRAGAN: I think the question was compared to each other.

DR. MITCHELL: No, I understand that, but one has to look at the cost to pregnancy registries as well and the costs generated by any signals that are generated or false positives or true positives, whatever they might be. So I

think it's a very difficult way -- it's a very difficult question, but I think the -- if one were to talk about the cost of individual pregnancy registries, which is substantial, and as Tina points out, and as Susan points out, that they -- the costs -- the economies of scale that you achieve in some of the alternative approaches need to be compared, so it's not an easy thing to do.

DR. STAFFA: This is Judy Staffa. I just want to also chime in on this. As you have heard from the speakers, FDA has provided support for some of these systems. So we have provided some support to DoD to begin to build their infrastructure, and we've provided the initial funding to get MEPREP off the ground. And that's substantial. There's quite a bit of cost there.

Our goal, though, was hoping that if we built this infrastructure, that the individual studies would then cost less and be, you know, more timely. And I'm not quite sure we're far enough along to know whether that's the case, because as we saw with the sulfonamide study,

there's still issues of having to validate these outcomes.

Much of the validation work that's been done in claims data are on adult outcomes, not that much on babies, and so we still need to take that step and, as Craig said, that's often the most time-intensive and sometimes expense-intensive part of the study. So I think we remain waiting to see, if we build these infrastructures and invest those funds upfront, how much will we reap in the long run?

DR. DAVIS: Can I chime in just for one second? So in the Vaccine Safety Datalink project, when that first started, I think it was three and a half --

DR. STAFFA: Just to be clear, this is Dr. Davis, for the record.

DR. DAVIS: Oh, sorry. Just butting in. It was three and a half years before the first study came out of the big VSD project. And, you know, there's just -- the infrastructure is really quite sophisticated and cumbersome, and that

investment does take a long time to pay off, as you see. But now, with the economy of scale, they're doing 20 studies at a time, and so I think everybody would say it pays off in the end.

DR. STAFFA: Thank you, Dr. Davis. And Dr. Conlin, I think, wants to make a comment on this?

DR. CONLIN: Certainly. My Birth and Infant Health Registry is funded by the Department of Defense, and although there were some additional costs to set it up, but now the maintenance of it and the process improvement that we do year to year is relatively small. We do this with a small staff of government service and contract employees of four to five individuals.

So when something like H1N1 came along and we were asked to try to do something quickly, that was very inexpensive for us, because we had all of the infrastructure. It was much less expensive than trying to start something fresh and new, comparing to our active registries, that, as everyone knows, are very costly, and especially

for the number of enrollees that ultimately result from that, the price is magnitudes higher than our large data registry.

DR. STAFFA: Thank you, Dr. Conlin. Other burning, smoldering, clarifying questions? Dr. Greene, another smoldering question?

DR. GREENE: One other question I'd like to address to the group of speakers from the DoD, if I could, is you're in a unique position to assess indirect exposures from -- to unusual circumstances and environmental situations on pregnancy among women whose husbands -- or fathers of babies, to be more precise, I suppose -- are exposed to unique circumstances. How important have you found any findings from those, quote, indirect exposures?

DR. COSTER: I think I'll turn -- if you're talking about the father's and/or mother's exposure during -- I'll probably -- that would not be gathered by the database that we're using because it's really EMR and claims data. I'll turn that over to Ava to answer.

DR. CONLIN: Yes, we include both infants of the military women as well as the dependent spouses of the military men. So in many of our studies, we've included both. In that population, I would say results overall have been reassuring. We did that in particular with both our women, who were overseas and exposed to the open air burn pits as well as the fathers of the infants that have that exposure.

We can also do that for vaccination, and most of our studies have focused on both of those. In our active registry, we did include women who were secondarily and -- secondarily exposed and laboratory proven to have been exposed to their husband's smallpox vaccination sites.

So in all of those cases, we've been able to do both, and really haven't found, I would say, anything of concern of those military-unique exposures that the service member father of the baby had been exposed to. But that really is the majority of our population. Eighty-five percent of our infants are born to those dependent

spouses, so many of our questions are coming from that population, and it's important to be able to accept that and accept it was well as possible.

DR. STAFFA: Thank you, Dr. Conlin. So I'd like to move to the first discussion question. Can we pull up that slide? The first question is really -- where I'd like to focus our discussion for the first few minutes here is how -- I know some of this was pointed out by a presenter, some of our presenters, is how can these alternative or complementary types of study designs -- do you see places where they might be particularly useful as complements or alternatives to a traditional pregnancy registry? And I know there were a few that were pointed out earlier, but do folks have thoughts after listening where these kinds of approaches and methods might have particular advantages over the traditional pregnancy registries? Yes, Dr. Chambers?

DR. CHAMBERS: I can think of a recent example where I think they might have a place that we weren't able to fill, which is in things like

teen pregnancy, where it's very difficult, from a registry perspective, to be able to enroll subjects who fit that certain special category.

But, generally speaking, my opinion is that the alternative study designs are complementary and that none of them uniquely replace the other and that the complementarity of them is actually the strength.

DR. STAFFA: Other comments?

DR. MITCHELL: I'm happy to give my talk over again, but I think my point --

DR. STAFFA: Dr. Mitchell, I think you deliberately snuck a peek at this question and framed it very nicely in your talk. Thank you.

DR. MITCHELL: We were challenged to do that, I thought.

DR. STAFFA: Other areas or examples that people would like to comment on from their experience where they've found these kinds of complementary approaches very useful? Trinka?

DR. COSTER: Yeah. I think on ours, where we did our -- it's in preparation -- it was

actually neonatal syndrome, and the -- going back to -- actually looking at diversion as a possibility, where you link it to the father's, and you're not so much interested in the father, whether he's related or not, but, really, asking the question, "Who was using the opioids," and then looking at is it the mom that's using it, or is it the father?

So I think those kinds of questions are interesting in that you could explore and then also make recommendations to the healthcare organizations on how best to look at those and address those problems.

DR. STAFFA: Thank you. Other comments? Anyone on the phone have a comment?

DR. CONLIN: I would just -- this is Dr. Conlin at NHRC. I would just say that I agree that the two, the active versus these alternative approaches, are very much complementary and I think can even be used for some of the limitations we've talked about with the active registry, such that we have lost follow-up. If you can use your

active registry participants and you do have loss of follow- up, if you can match them up with some of the electronic data that you might find from these alternative big databases and see that there's consistency between what you're finding in the active registry and what you're finding in the large database, it would seem reasonable, then, to extrapolate for your loss of follow-up, that you could maybe rely on some of that electronic data to somewhat backfill or fill in some of that lost follow-up data that ends up limiting your numbers and what you can say about your population.

DR. STAFFA: Thank you. Dr. Yao, did you have a question?

DR. YAO: I'd press the panel, maybe, a little bit harder, and I think we've all heard that there's generally interest in describing that there would be ways to complement a pregnancy registry, recognizing the limitations, the advantages that we discussed yesterday.

But, you know, where I see the utility is when we say, okay, we have a question, as Dr.,

I think, Mitchell very nicely illustrated this morning, that you have a question that you're not sure about, and here is a large database that is case-controlled, so the limitations with sort of that retrospective, but it's large, and you kind of filled that hole.

But, you know, I can envision, as many cases, and we've experienced before where one dataset points you one way, the other dataset points you the other way, and you're still sort of stuck. And then we have to kind of weigh the evidence of which one's got greater power, which one has less, and how do we go? So I would really like to hear the panel's comments on how you would use this in a systematic way to help answer the question.

DR. STAFFA: Dr. Chambers, did you have your hand up, or were you just waving?

DR. CHAMBERS: I think that's exactly the direction that you need to go, and what you describe, the differences in results is the reality of doing public health research. So it

happens independently, and it happens even within your own dataset. You could look at things like the National Birth Defects Prevention Study. You could look at it one year, and five years later, with a bigger sample size, you may find a different result.

So but in answer to your question, I think that the strength is to do this in a systematic way so that you approach addressing the questions looking at them in multiple complementary approaches, and then, as scientists who deal with this stuff all the time, you have to try to determine what, in fact, you can pull out of that that makes sense.

And some of that goes back to the kind of methodologic issues that I think Dr. Conlin was bringing up, which is are there also methodologic activities that can go on that address why is it that you're getting a different result using a claims database approach versus a claims control approach? Is it that you didn't have the folic acid information? Does that contribute in this

case? So I think better understanding of why do you find differences is also a benefit of having a systematic approach to using multiple data sources in a much more organized fashion.

DR. STAFFA: Dr. Berliner, did you have something you wanted to contribute?

DR. BERLINER: Yeah, I mean, I was going to say similar things. I was sort of saving my comment for Number 2, but since you brought it up, that -- you know, I think like when I was listening this morning, each individual dataset is impressive and method is impressive by itself, but what is the synthesis across it? So my question is would you get the same answer in each database if you asked the same question?

And, you know, I think it's -- I don't know if it's even too obvious to say, but, I mean, we really have a power problem here with any individual dataset, so we need every single patient with any kind of data that we could get about that patient. So, you know, I think that the next steps really are to validate all these

different datasets against each other. Really -- as Tina said, really look at if there are differences in results, why those differences are, and then how they can all be synthesized together.

DR. STAFFA: Well, thank you for the beautiful segue to Question 2, which is, again, as we've heard, you know, you heard from the industry folks. You know, they're tasked with this many times> Particularly when a new drug is approved, they're tasked with going out and trying to launch investigations to try to answer questions and to understand what's going on. And some of these data systems, such as MEPREP and such as some of the DoD systems, are not really accessible to them to do.

Knowing that FDA doesn't -- is never going to have enough money ourselves to be able to mount and address all the safety questions that exist, I wanted to just get your thoughts on how do we think about making some of these -- I guess if you -- for lack of a better word, turn these into more societal-base type resources, and what

would that look like so that multiple groups, whether it was academic researchers, industry researchers, regulators, public health authorities, would be able to actually use complementary type of systems, along with pregnancy registries that are launched individually, to begin to put together a portfolio to look at safety?

Thoughts you have on that, particularly from the folks who've had some experience with this?

DR. MITCHELL: Well --

DR. STAFFA: Dr. Albano?

DR. MITCHELL: Oh.

DR. ALBANO: Oh, thank you. I just wanted to say, from a pregnancy registry perspective, I think one of the ways that some of these alternative sources besides their research aspects that they can help with the pregnancy registries is helping to understand the drug utilization, so how many potential pregnancies are exposed that we can, you know, expect to be in the

population, as well as to hone in on the specific types of healthcare providers that might be targeted for the awareness efforts? So kind of complement the registry to do a better job of finding the patients and enrolling them.

DR. STAFFA: And Dr. Mitchell?

DR. MITCHELL: Yeah, I was going to make the point that one of -- I mean, I think, as I tried to explain, that the origins of VAMPSS was exactly to resolve the issue of the limitations of pregnancy registries and to combine it with, obviously, a large case control program, which has limitations like every other study. But in terms of our own governance, we've been able to work very efficiency with industry and with regulators, through the advisory committee system and that sort of -- I'm not sure, beyond that, that -- I mean, we have very positive experience in what we're doing, and I think that the industry sponsors have been very satisfied with the arm's length relationship that they have. I think the regulators and the public have similarly been

satisfied by that arm's length relationship.

I'm not sure how you bring it all into a common system. I think certainly your first step is in identifying what options are available and also, as Sara Ephross and some other people mentioned, trying to establish -- I mean, we don't have qualified tools in the post-marketing environment. People in the pre- marketing environment are familiar with these. But I think it would be very helpful if FDA were to set up some guidance and standards so that sponsors would have the ability to anticipate what kind of programs might meet FDA requirements for their post-marketing obligations or even if they undertake them without an obligation? And I just would encourage that.

And then just one other point which I want to -- I think it's well-appreciated, but I think we need to be careful in the balance between power and validity. People who work with me know very well that I am constantly reminding people that when there's a debate, validity wins all the

time in my view.

And I think that we can't simply look at the size of the study, whether it's our study or someone else's study. One also has to really look at the validity, because, you know, big numbers with invalid conclusions are not terribly helpful.

DR. STAFFA: Thank you. And I think -- this is Judy Staffa, for the record. I just want to comment on your statement about wanting -- the desirability of FDA issuing some kind of qualification for different methods or resources.

We -- I think we have put out some guidance which I think is relevant here, which is a guidance we issued about a year ago, in May of last year, about doing safety studies using electronic healthcare data, which was specific to claims and electronic medical record data. So with regard to approaches that use those kinds of data, I don't think there's any reason to not be looking at that guidance for at least some direction as to what FDA's looking for studies that are done and submitted by companies or going

to be used for regulatory decision-making and what kind of information we want to see to be able to do that.

So even though that doesn't set out standards per se, it is guidance that lets companies and folks know what kinds of information FDA's going to want to see in evaluating that work, and that can be built in upfront.

DR. MITCHELL: The question I'd have -- and I'd really pose it to the people who have worlds of experience, and you are among them -- in using electronic claims or other data, that clearly the world of pregnancy is very different in these datasets, and huge amounts of efforts have to go in to making those datasets appropriate for pregnancy, effort which may not be necessary at all for other, you know, if you will, non-pregnant situations. And I don't remember how much of the guidance went into that issue of pregnancy, because that's clearly --

DR. STAFFA: Yeah, it doesn't speak to pregnancy per se, but it does speak to validity of

outcomes and validity of exposures, and I think that's what you heard being addressed in a lot of these presentations today, is trying to verify the validity of things like pregnancy. Is someone actually pregnant? And then also the validity of the outcomes in the babies. And, again, even in mothers, if that's the health we're interested in. So other comments on this? Dr. Hagan (sic)? Cragan, sorry.

DR. CRAGAN: That's okay. I want to echo part of what Dr. Mitchell said in the beginning. I think in the years since the guidance on pregnancy registries came out, and since FDA started to sometimes make that a post-marketing requirement for approval, there's gotten to be sort of -- it's almost a knee-jerk reaction. There's a concern about use in, you know, women who may be pregnant or reproductive age women. Well, let's do a pregnancy registry." And that's sort of the common, immediate response, and that's what the company does. And I hear that occasionally on advisory -- FDA advisory

committees that I've been a part of, where there's not a lot of expertise about pregnancy, so it's, "Well, have the company do a registry."

And so I think if there can be more discussion, perhaps more guidance, on -- you know, that that's not the only method, that there are some systems out there that can combine methods to do a more comprehensive approach, can look at things better that have set of quality (ph), if there are ways that FDA can encourage companies to buy in to a part of that or be a part of that for the drugs that they're required to monitor, rather than setting up a registry that has been done for so many others that may not hit the quality or answer the question.

So I think if FDA can be -- play more of a role of broadening the range of activities that can occur as a post-marketing requirement, that might be a benefit.

DR. STAFFA: Which brings us back to our Question 2, which is I think FDA can take that -- can certainly hear that, that FDA can present

industry with, "You shouldn't just be thinking about a pregnancy registry. Let's talk about all the options." So let's get back to how -- what are the kinds of systems that might work so that these other options could also be available to industry? Yes? Dr. Dana?

DR. DANA: Yes, this is Adrian Dana. You know, I do think that this is the potential, you know, promise of the electronic medical record, of looking at -- and maybe, you know, FDA, in concert with CDC and other stakeholders, to first of all figure out if we can, in a systematic way, collect pregnancy data and drug exposure data and adverse event data in these electronic medical record forms, and then, you know, have some way where we can pool this data so that we can get large numbers.

You know, we still -- despite everything, we still have the issue of what's the appropriate control group? And if we had a larger, you know, more diverse database, you know, we might be able to approach a reasonable control

group.

I would also think that over time, we need to think about this, rather than in a risk paradigm, in a benefit-risk paradigm. So maybe that's not as true of a vaccine that doesn't really have to be used during pregnancy, but I think it is absolutely critical in things like hypertension drugs or asthma drugs or anti-inflammatory drugs that do need to be continued. So if you had that EMR, you could do a benefit-risk; not only what happened to the pregnancy while the woman was on this drug, but what happened to the woman and her underlying disease while she was on this drug and pregnant?

So I just think that we do need to -- I think we're on -- in a time when we have promise of this electronic database, and we should design the database so that we can also get our answers, not just, you know, record for patient care.

DR. STAFFA: Dr. Greene?

DR. GREENE: One question or issue that came up in my mind as I was listening to the

discussion here, when discussing validity, as Allen was and as you were, both of you were really referring to internal validity, and the other issue is, of course, external validity. And there was a question yesterday asked about the National Children's Study. And the National Children's Study -- I was on the scientific advisory board early in the Children's Study when they were going through some growing pains in terms of figuring out how to recruit patients.

And they started out with a plan, okay, that would ensure a population-based recruitment that would have external validity, and the ideal bumped up against the real, which was that they were -- they couldn't meet their recruitment goals, and it was spectacularly expensive. And then they had to face the reality that they needed alternative recruitment strategies to enroll enough patients, but, unfortunately, that may be at the expense of external validity, because they're no longer truly population- based.

And that same problem may be encountered

by some of these alternative approaches, because, as was pointed out yesterday by Lew and Sonia Hernandez, the people who enroll in pregnancy registries are not necessarily representative of the general population; therefore, speaking to limited external validity.

DR. STAFFA: That's a great point. Dr. Conlin, did you have a comment?

DR. CONLIN: Sure, I can follow up on that a little bit. My comment was to an earlier comment, but I think with our military population, that sometimes questions the external validity, especially among our active duty women. They tend to be younger, healthier. Our dependent spouses, not so much. They're more representative of the general population, although they do all have equal access to healthcare. But that, in and of itself, has provided an interesting opportunity to look at things like racial disparity despite equal access to care among a diverse population.

My original comment, though, was back to the one about comparison groups and how these

large databases do allow us to oftentimes use multiple comparison groups, which we have done. It's easy to say we have a group of vaccinated women and then unvaccinated women, but how do they differ as far as being healthier because they're seeking these recommended vaccines? Or, in our case, we have our deployers and our non-deployers, with our deployers tending to be healthier because they're eligible to deploy. We have those that are stationed overseas that go through additional screening and tend to be healthier.

So it's not real easy for us to find the exact best comparison group, but we can, then, look at folks that may have been vaccinated with another similar vaccine or one that's considered safe or look at some other timing of vaccinations or exposures, pre-pregnancy, post-pregnancy, and then use those as multiple comparison groups to try and get a well- rounded answer to the question that we're asking.

DR. STAFFA: Thank you for that comment. Dr. Chambers?

DR. CHAMBERS: Adding to that, I think one of the advantages of these alternative approaches as opposed to a single-drug pregnancy registry is the idea of looking at relative safety for various treatments that might be used for a particular indication, which is, as we've heard from the public comment, that's what the patients want to know and what the providers want to know. And I think in the antiepileptic literature, there's actually been a nice publication that's actually showed by dose, by drug, the relative risk for specific birth defects and birth defects overall, which really is a powerful message for clinicians.

So to the extent that you can get to the point where you can look at alternative asthma medications for the same underlying condition, that that provides an additional benefit using these alternative approaches.

DR. STAFFA: Dr. Berliner?

DR. BERLINER: So one thing that I sort of -- you asked this question about funding, where

is the money going to come from? And, you know, so I'm not even sure exactly what question we're asking, because I've heard a lot of different things over the past few days about, you know, FDA is requiring follow-up on some drugs, but not others, but that maybe patients are interested in other drugs, like even over-the- counter drugs; that, you know, what's the right outcome? Is it congenital abnormalities? Is it, you know, behavioral problems in kids six years later? You know, there's a whole host of health issues that were discussed, and -- and, you know, so, I mean, everything that you're adding is going to cost more money, and -- and then -- so I think that there needs to be some kind of priority-setting, like from a public health point of view. You know, what question are we really trying to answer, and then what data sources do we have, and then who has funding to contribute and what are the incentives?

So are companies only going to contribute where they're required by FDA, or, you

know, do they have a public health incentive? You know, then what kind of governance structures can you set up so that there's -- you know, you're giving all stakeholders an equal voice and avoiding conflicts of interest?

So I think -- you know, I think that to move forward, we really need, you know, all those steps. We need a priority-setting, we need to figure out what our resources are, and then we need to figure out how to match the resources to the priorities.

DR. COSTER: I would like to just comment. I think --

DR. STAFFA: Dr. Coster?

DR. COSTER: Yeah, I think it is a little difficult when you are a healthcare provider, such as we are to the Department of Defense. We have -- we're supposed to have a very fair way of purchasing our, you know, hundreds of millions of dollars of medications. If you support one drug company, you're really showing a bias. And so I think that the VA feels that way.

I know the Department of Defense feels that way.

And you have to therefore, you know, figure out how do you -- how do you support a new drug that's coming on the market? Yes, we're very interested in it. Is it going to squash the competitors? And so -- and you're going to probably compare it to that competitor. So we've not taken funds for that. You know, the question is, is how do you -- if the sponsor wanted to get that information, how do you filter it through so that we're not biased by the subanalyses that we're going to do and all those things to make sure that our analysis really fits our patient population and that we can ensure that we're not biased over one company over another?

So I think there's a lot of difficulty, I think for certain organizations to be funded by a drug company for a product where there's another drug company that does it. I think it raises, then, access to those data sources. So those are just difficult challenges, I think, on how to best get the information to the drug companies that do

deserve to know what the safety of theirs is, but also to perform it in a way that we're not biased.

DR. STAFFA: Can you talk about -- those of you -- I think it was Dr. Mitchell and Dr. Chambers who've been working with professional societies. Can you talk about their role, what role they play in the collaboration and the partnership?

DR. MITCHELL: Yeah. I think really on two levels. The first role is the Quad AI, the American Academy of Allergy, Asthma and Immunology. And they are really the parent infrastructure providing organization, if you will, for the VAMPSS effort. And in addition, as part of our advisory committee, we have representation from ACOG and the Academy of Pediatrics as well, and as well as -- as I mentioned in the slides, as well as some federal agencies and so forth.

So it's in that way that they are participating in the activity. So the Quad AI is really the primary practitioner group involvement,

but we bring in the two other groups that are so critical, ACOG and AAP, into our advisory committee process. I'm not sure I'm answering your question.

DR. STAFFA: So what role do they play? What specifically do they do? Do they send out communications to all the practitioners in their society about the existence of this? Do they provide funding? Do they sit on the board? What is their role?

DR. MITCHELL: Yeah. There is no board. The -- there's a sort of complicated structure, but simply put, the Academy of -- the Quad AI, OTIS, and Slone represent the sort of active component of VAMPSS. Funding in kind is provided by the Quad AI, but no funding is provided by the other practitioner groups.

They do assist -- and Tina can speak to this -- the solicitation competitor that the practitioners can offer is really specific to the registry activity. And Tina can talk about that. And they do certainly participate in that

activity. But there is no -- their involvement in the advisory committee is to help guide the design data collection analysis, and they -- I can tell you -- Tina and I can both testify from personal experience that the advisory committee, which, in the case of the influence vaccines, has been shared by Peg Honein, has provided incredible amounts of very useful information, which significantly affected the end result of the study. So they are very active. Tina, you might want to comment on the other.

DR. CHAMBERS: Yeah, I think the practical aspects of it are they have a Web page on the Quad AI website that's specifically devoted to VAMPSS and describes the whole project and describes it as a activity of the Quad AI. They produce -- they host a booth in their member area for us that we exhibit at and distribute materials at at every annual meeting. We have a workshop at every annual meeting where we present what's happening with VAMPSS for attendees at this.

And then they do -- they engage, on our

behalf, with other practitioners who are not physicians, other groups who have allergy and asthma, in order to engage them to know about the cohort part of the study. So they actively help with recruitment and then provide mechanisms whereby, as information is developed, we can feed it back to the practitioners.

DR. STAFFA: Other comments or questions? Thoughts? Anybody on the phone have anything they want to share at this point? Because we're coming to the end of our time. Any final thoughts on this section? But I'm sure more comments will come up in the next one. Yes, Dr. Chambers?

DR. CHAMBERS: Could I just add one pet peeve of mine, and Dr. Dewulf mentioned this. Not that it's an alternative model, but something that I think is a missed opportunity are the number of women who inadvertently become pregnant in clinical trials. And this -- you know, it's never a -- well, unless maybe in the case of something like a vaccine, but it's typically not hundreds of

pregnancies, but there's numbers of pregnancies that do occur.

And I think they're, to varying degrees, followed up or not followed up very proactively in clinical trials, and I really do think that that's a missed opportunity for pharmaceutical companies to get better follow-up on all pregnancies that occur in the course of clinical trials as sort of a nucleus of information that's the very first information that's typically available in humans.

DR. STAFFA: I think that's a great point. So at this point, I think we're going to be transitioning to Topic 4; is that correct, Dr. Tassinari? I would like to encourage, if possible -- our third question, we didn't really get to, but I think it could be included under steps forward of what to think about for the future, is are there other models, systems, approaches that people have thought of as they've heard the approaches that have been talked about today that might also be explored for the future?

I think we should think of this as not

the end of the discussion of these different kinds of methods, but rather just another step on the way of how do we get to another step? I'm so impressed with what I hear about things -- and I consider myself a person who's fairly plugged in to this arena, but I've heard things that are going on that I wasn't aware of, and I'm so pleased to hear of all of these new ideas and activities, and I hope we can keep the progress going, and I hope the fact that we're all here today, we can continue -- now that we know who each other is, we can continue to talk to each other, have offline conversations, and begin the process of how do we work together, how do we collaborate, and how do we bring these systems to another level to really allow the kinds of complementary work to go on that I think we all agree needs to be done? So I thank you all for your time and attention. I'll turn it over to Dr. Tassinari.

DR. TASSINARI: Thank you very much. I think the -- this was -- this session is really

designed to have all of us sit back for a minute, take a deep breath, think about the very busy day and a half that we've had here, with a lot of good information, just as Judy has articulated. Can we move to the next slide, please? Okay.

I just wanted to remind everybody a little bit about where we started as sort of a basis for where we're going to finish up. The objectives, after a lot of conversations and a lot of hard work from many folks within the agency, were to bring you all together and bring this audience together to think about how we approach getting this very important data for a population of people who need information when medications are essential for treating their disease, keeping them healthy, and they happen to be pregnant.

And so we looked at this, and our objectives were really around looking at our existing set of recommendations to find pregnancy exposure registries, and we wanted to know how well we were doing. So we took a look, and we wanted to, by the presentations that we had, talk

a little bit in more detail about where we are and what the current status of our process are. And I think yesterday, we learned a great deal.

Connected with that, of course, are to identify any strategies for improvement, because anything that is good probably can get better. And then we spent a good deal of yesterday afternoon talking about some of the real hard issues around making these pregnancy registries successful. And that's in the basis of the outreach and communication, and I think we had a lot of good conversation there about where we could possibly go and what to do.

And then today and this morning, I think we've had some really fascinating presentations about all the options that are available for now for what I think are better described as complementary approaches and not alternative, so I think that's a learning for me today. I think the words are going to change. And so we still need to move forward. And so -- if you'll move to the next slide, please.

These questions are really around where do we go? With all this information that we just collected, and we -- on all this great brainpower that we have here, what I'd like to do is give each of the panelists an opportunity to think about maybe the top two impressions or the top two recommendations that you have for us to move forward. What are the most important things that you would like the FDA to take back after this meeting and move forward and facilitate, if you will, the kinds of activities that are going to improve this data collection that we have?

So with that, I'm going to pause for a very quiet ten seconds or so, and then I'm going to pick on somebody to start, unless somebody wants to volunteer.

MS. MOYER: We can pick somebody on the phone, if you'd like.

DR. TASSINARI: I can pick somebody -- is somebody ready to say something? Yes. The phone -- you're not -- you can't escape if you're on the phone. Michael, do you want to start off?

DR. GREENE: Yeah, the first thing that comes to my mind is that I would like to suggest that the FDA -- and I'm not sure -- you guys would be better off figuring out exactly what group, whether it's Office of Safety or CDER or Office of New Drugs, whatever -- begin discussions with the relatively few providers that dominate the electronic medical record market. There's a relatively small number of very large electronic medical record providers out there that are going to provide the electronic medical records for the vast majority of patients in the United States. And I think it would be nice to start talking with them sooner, rather than later, about what you would like to see and what would be beneficial to society to have built in, baked in to these electronic medical records, both in terms of prompting functions, of asking providers to provide specific information, as well as menus for coded information for dictionaries so that you're not trying to search through using natural language progressing, which is good, but

inevitably less precise, that would help us to assess the potential risks, or benefits, for that matter, associated with various exposures in pregnancies, whether they'd be medications or vaccines.

I think -- you know, there have been several people who have spoken about electronic medical records, and I don't know the degree to which the FDA has been involved in that. I know that the FDA has mandated certain things in electronic medical records, such as signatures in electronic medical records, authentications of electronic medical records. I don't know how much ability you have to mandate these things versus to request these things versus suggest these things, but that would be my first suggestion for the near future.

DR. TASSINARI: Do you have a second one?

DR. GREENE: No, but give me another 20 seconds.

DR. MITCHELL: It's Allen Mitchell. I'd

volunteer. I think we need to think of FDA, not just as CDER, but CBER, and perhaps Devices as well. And I think CBER has actually made a lot of progress in this area, and there's a lot of lessons that can be learned from it.

I think that -- I would respond to your challenge with two points. First, I would suggest that a registry be paired with some complementary approach that can tackle some of the issues that are inherently limited in registries, and that complementary approach can be a variety of options. Obviously, we're involved with one, but others are involved with others.

I also would argue that, independent of the guidance for electronic record research, I think a specific focus of FDA ought to be -- and your group plays a critical role here -- is to define accessible standards for these kinds of approaches.

And, while not a recommendation, I think that it's useful to think in the short versus longer- term horizon. I think all the ideas about

using electronic medical record -- your idea, Michael, and others' -- is certainly not going to prove very fruitful in the next three to five years, but I think it's a long-term horizon that's a critically important thing.

But I also think -- and I think I'm reflecting both a regulatory perspective and a sponsor perspective -- is that we're in the here and now. And tomorrow, when a company sits down with FDA and there's a discussion about pregnancy safety of a product, old or new, you know, I think the FDA has to be in position to be able to say, "Here's what we find that's available now that you might want to consider using to meet your -- either your obligation or your voluntary commitment."

DR. TASSINARI: Thank you. Anybody else ready to go? Trinka?

DR. COSTER: I'll take two. One is on the first one. If there is a voice for improving electronic medical records, it would be the -- in the pharmacy data transactions systems that

connect with the electronic medical records, is to capture indication. Right now, there is no -- for medications, no way to really tell indication. You could look back for, quote, ICD-9 codes, but as you know and I know, that's still a guess. And so it would be a requirement that medications in a transaction actually have, as part of their regulatory requirement, is the use of that drug be indicated on the label or whatever, because if it's in the label, it's in a data system. If it's in a data system, we pull it. And that would really assist us in really knowing why the drug -- really know why the drug was being used.

A second is the -- you know, how we capture adverse events, intolerance, and drug ineffectiveness. Right now, most people use a patient safety reporting system to put those, and they're oftentimes standalone or sometimes can be part of their medical system. The allergy section is really -- is -- also communicates with your drug system to know if there's drug-drug interactions, et cetera. If we thought about

allergies as being true allergies, where people document true allergies, where people document drug ineffectiveness, and where people document drug intolerance, now you're really capturing a method to get that information that's within that electronic medical record and not have to have standalone systems. So that's one.

A second would be to -- we have the National Sentinel. One concept is if we did do -- you know, one of the things we had talked about in the National Sentinel is, you know, these drug utilizations, where you just send out, you know, a query that everybody's kind of developed of, you know, who's on -- how many people do you have on this drug, what are their age, distributions, how long they've been on it, are they on this vaccine, et cetera, or are they on -- are they pregnant on this vaccine?

And then, basically, if we, you know, put that into a system, you now have -- you can see across the nation who are your players that move to the next part, which is no longer drug

utilization, but maybe do you have, you know -- feasibility? Do you have enough outcomes on this? And so -- and you eliminate those that don't have enough players on that drug. They need to have -- you know, they need time to cook, so to speak, to get more players on that drug.

And then, you know, once you have those players that are -- have enough people -- enough population on that particular drug or vaccine you're interested in, then having a set protocol, so to speak, or methodology that one wants to, you know, do a study behind their firewalls, enables them to then do that analysis, and then if they want to share, in an aggregated way, that strips (ph) where the healthcare system that produced that comes from, then you actually could start, you know, imagining that you could then, you know, have folks be able to see those kinds of results, including pharmaceutical companies, that could get some of that information that they couldn't get other ways.

And, you know, whether you centrally

fund that, that people could say, "I just need one FTE for this particular SAS coding or something that we're doing," that -- I could imagine that you could do it in a way that doesn't infringe on my ability to do it in an unbiased way. We've kind of agreed that these are the covariates that we want to look at. We've agreed that, you know, this is the age distribution that we're looking at, and we're going to, you know, all share our results, but strip away where that -- those results came from so I can't get a FOIA (ph). So that's it.

DR. TASSINARI: Great. Thank you very much. Any -- go ahead, Jessica.

DR. ALBANO: Jessica Albano. I just wanted to say that, you know, I think that, you know, all of us obviously have expertise in one or more of the approaches that we've been discussing, but I don't think anyone particularly has expertise in all of them. So, you know, it may be a good place for, you know, the agency to lead the effort in evaluating the different possibilities,

to set priorities, and then communicate them with clear guidance. I don't think anyone wants to see, you know, a situation where, you know, there's too many options and not enough direction, and then it leads to confusion and uncertainty about what the best approach is.

DR. TASSINARI: Jan?

DR. CRAGAN: I think in the immediate future, if revision of the guidance on pregnancy registries is in the offing (ph), I think what it does now, the way it was originally set up, it presents -- lays out the issues and says, "Here are the things you need to consider, and if you do this, you may have some biases, and if you do that, it'll be different," and whatever, and it takes on the tone of a manuscript that says, "Here are results, and here are the strengths and weaknesses of that," you know. And it's very easy to say, "We'll collect some data and just explain what the limitations are."

So I think that in your revisions to the guidance need to have more of a -- not so much,

"These are the issues you need to think about," but, "These are the things you need to do to avoid those issues." It needs to be more definitive in terms of what should be done. And I think that can include a discussion of these complementary approaches and sort of set the stage for that as a way to go forward, rather than, you know, just the registry itself. So that's one thing.

One other thing I wanted to say is that I think this meeting has been very productive and very helpful, and I've very much enjoyed having all these parties together to talk about what's going on and share what's happening, and I would encourage you to do that on a more frequent basis.

DR. TASSINARI: Yes, Craig?

DR. HANSEN: Hi, this is Craig Hansen. I'd echo what Jan says. It's been a great meeting, and thank you for having me here. I'm going to be a little bit self-involved here, as coming from the angle of a soft money researcher, because all these ideas are fantastic. We have all these data sources. We can do all this

wonderful research. But at the end of the day, we need funding to do this, and that's very difficult.

As you know, funding is getting tighter and tighter. You look on NIH websites for funding announcements to do with this topic, and they are very rare. And so I don't hear any discussion about funding or potential funding or sources of funding for the future to keep all this going. Obviously, I'm coming from the MEPREP angle there. So I think it would be good to include that in part of these meetings as well.

DR. CHAMBERS: Tina Chambers. I agree with you totally, and that kind of speaks to the issue of having a select group of qualified approaches, where there's, you know, a critical mass of groups that can maintain sufficient infrastructure to be able to address these issues and not have to, you know, sort of struggle between projects.

One thing that I -- to add to what Allen said about pairing a registry with another

complementary method, another approach that we've taken that I think is really reasonable for new drugs, where it is unknown what the prevalence of use will be in pregnant women or who's actually going to get prescribed it, that when a new drug post-marketing commitment or requirement comes into place, that maybe there should be a preliminary Phase I period where the registry and the complementary approach actually get a couple years of experience of what the use of the drug is in the population; how many pregnant women are exposed, inadvertently or not; what are the indications it's being used for; and then re-look at the whole landscape again, after that two years of new drug experience, and design what the forward path would be with the complementary approaches to address that issue that actually has some teeth in it.

DR. TASSINARI: Thank you. Ooh, I've got to call on people now. Susan?

DR. ANDRADE: Hi. I actually agree with everything that's been said so far by the panel,

and I just want to reiterate what some folks have said about exploring more with electronic medical records, because it comes -- it might be helpful from, again, all these different angles, whether it's recruiting for a pregnancy registry, whether it's getting more information, whether it's getting better information.

I also -- again, following up a little bit about what Craig had mentioned with funding, I knowledge we've been going through this with MEPREP about the different governance issues, and it might be nice to get all different stakeholders to see, you know, not only their needs, but how acceptable it is and how much they really would value some type of relationship, like you have with VAMPSS, where, you know, it's more of a private endeavor, where folks can actually give the input.

And I don't know how much FDA goes to industry or how much they go to other different professional organizations -- and just kind of get the feel. And I think this is a good start,

because we've actually heard from a lot of the folks today and yesterday.

DR. TASSINARI: Thank you. Adrian?

DR. DANA: Yes. Well, I do want to reiterate the issue, and I know it may be long-term, but I think the time to get in on the EMR is now, if not a little bit late, and then it's very important that we standardize that, and as part of that effort, I think that there needs to be some standardization of definitions. And I was struck -- I think it may have been Allen this morning. He said they used their own drug dictionary. You know, that's a very basic thing, but if, you know, we're all calling the same drug 50 different things in the database, you're not going to find it.

So I think that efforts around standardization of not only definitions, but how we enter data into these large databases, will be hugely helpful, and that's the sort of thing that would have to be directed at the level of the FDA. I don't know who else can really do that.

The other things is I do agree that an updated guidance would be helpful and that -- and that I think that perhaps we should think about these -- the methods that we're talking about in terms of whether they're signal-generating or signal-confirming so that, you know, you might plan in advance to use a couple of methods to try to find a signal, and then design the signal confirmation method differently, depending on what you find out of signal generation. So that's sort of another way to think about the guidance.

DR. TASSINARI: Thank you. Yes, Sonia?

DR. HERNANDEZ-DIAZ: Before you call on me -- I don't want to repeat many very good points, but just to highlight what Tina said, that I think it's great, just the fact that we are considering that a registry doesn't have to be the only thing to consider, and there may -- there are some validity and power considerations to decide which design may be the best one. And one of them would be the use of the medication, especially at the beginning in the population, so if it is very

rarely used, then perhaps a registry could be a more advisable method, but perhaps if it is more commonly used, other methods may be more efficient as valued (ph).

And -- but just to say something different, another thing to consider, maybe, long-term is the fact that Medicaid, Medicare are covering 40 percent of the deliveries in the U.S., and we from outside cannot access -- couldn't have access to the identifiers, but if there is a desire to do so, that data from CMS at the federal level could be merged with birth certificate, death certificates, and could provide to the FDA, maybe directly from CMS, some important information. It's another potential method to consider.

DR. TASSINARI: Thank you. Elise?

DR. BERLINER: Yeah, I don't know if I have anything to say that I haven't said already, but I guess the things that I would think are the priorities, you know, I think like we heard that even registries on the same topic don't always

agree with each other and that now we have -- we've heard about a lot of these different data systems, so really understanding whether we're getting valid data, you know, harmonizing the information across the different data systems, I think is a really big priority.

And the other thing is, you know, I think that one of the public commenters mentioned that there was only one patient voice here, and I think that we do need to have a priority setting that includes a lot more patient voices, and that, you know, we really need to understand, from a public health point of view, including the perspective of FDA, but also including the perspective of patients and providers, what are the priority questions to answer, what are the priority outcomes to measure, and then what resources do we have, both in terms of data and funding, and then how can we match that to build a comprehensive system?

DR. TASSINARI: Thank you. Diana?

MS. JOHNSON: Sure. I thought Julia had

a lot of really great points yesterday as far as outreach goes. I think that her points regarding trying -- and a gentleman in the audience today had also made some of those same points about bringing the studies to individuals and making it easier for people to find that information so they're not trying to do through it when they're already busy with many other things. So maybe considering changing registries on the FDA website to something that might be a little bit easier for patients to -- or subjects, pregnant women to identify with, and then maybe just highlighting some information in there regarding how beneficial this is to everyone.

DR. TASSINARI: Thank you. Our colleague is on the phone.

DR. NALEWAY: Hi, this is Allison. It's a little hard to build on to all the great things that people have said, but I would just echo the need for kind of thinking of this as a research portfolio, and, you know, making sure that you've covered signal generation and signal confirmation

and doing (inaudible) studies and surveillance, just thinking about -- you know, prioritizing within that larger portfolio of studies.

And then the other piece that really struck me today was how all of us have kind of worked somewhat in isolation with our EMR systems, but we all kind of came up with basically the -- a very similar approach in a lot of ways, and I think if we could work better with each other (inaudible) and maybe this gets to some of the public-private partnerships for funding and just even discussions within the agencies, that would be helpful, because I think if we could get some agreement on how to harmonize and streamline all of the infrastructure pieces for working with the EMR, then that opens up some opportunities to work with data sources that we didn't really even talk about today.

Well, I think someone mentioned, like, you could go out to the CVSs and the Walmarts of the world and get some of those data, bring them in, or, you know, a lot of us are starting to

build biorepositories at our sites. We could get into biologic specimen data and genomics type of questions.

So if we could just get some efficiencies, I think -- and (inaudible) infrastructure, then there may be some possibilities that emerge that we're not really even thinking about right now.

DR. TASSINARI: Thank you. Peggy or Ava?

DR. CONLIN: This is Dr. Conlin. I would agree with so much of what has already been said. But I think having the guidance that spells out what is ideal or in a best-case scenario, what would be available to evaluate some of these products, but then having a timely review process when something does need to be looked at, understanding the limitations and how the ideal might not be able to be met, just being able now with the knowledge that has come from this meeting to know what's already out there and available, maybe piece together (ph), on a case-by- case

basis, what should be done for each individual new product, and, really, what's feasible in these situations.

DR. TASSINARI: Thank you. Peggy, are you online, or do you want to provide any comment? I know she was having trouble with her --

MS. MOYER: Yeah.

DR. TASSINARI: -- connection.

MS. MOYER: Peggy let me know that she didn't have anything to add.

DR. TASSINARI: Okay. Great. Well, what's your second one? Yeah. I know. We could start (inaudible). But so sort of in a wider frame, is there anything that we, you know, in the course of listening to the other panelists or -- any other thoughts or recommendations that you have for today? Yes?

DR. HONEIN: Sorry. This is Peggy. I'm just not very skilled and managed to disconnect my phone while trying to unmute.

DR. TASSINARI: Peggy, do you have any comments, or are you --

DR. HONEIN: No, mostly I think everything has been said, and I think the only thing I wanted to echo was that having these a little more frequently, I think could really help everyone think about where different pieces fit together and how best to prioritize them together. So I would really encourage more meetings of this kind.

DR. TASSINARI: Thank you.

DR. MITCHELL: And I would just add -- Peggy's voice reminded me that we haven't really prominently mentioned the NBDPS and its successor, BD- STEPS, the CDC initiatives, and I think that's clearly one of the major resources available for looking at drug safety in pregnancy.

DR. TASSINARI: Any of my colleagues from the FDA at the table, any questions that -- lingering questions that you have? I'm looking at you, Pam. Did you -- do you -- are there any thoughts that you would like to canvas based on yesterday's topic to help you move forward?

DR. SCOTT: No, I think we've gotten a

lot of great suggestions in terms of how to improve the FDA Pregnancy Registry Web page to make it more usable and more user-friendly and also more available to healthcare providers and patients.

DR. TASSINARI: Michael, any thoughts?

DR. NGUYEN: I don't at this point. Thank you.

DR. TASSINARI: My goodness. We were rushing today. Are we going to wrap up?

DR. MITCHELL: I just want to reiterate something from yesterday, and I think that we're all talking about revising the guidance, but, again, I would urge that the use of the term "registry" be reconsidered, whether, you know, under a more global umbrella of assuring pregnancy safety or whatever, but that the registries component maybe can be given a different name, if, in fact, my anxiety about the term being a turnoff proves correct. And I think it would be worth looking into.

DR. TASSINARI: Very good. Well, I

actually would like to follow up on a comment that we heard from the public comment session this morning, just sort of as a -- it's a little switch in the topic, but I think complementary, if you will, and that is the dearth of information we have for women who are breastfeeding. And so I would like the panel's comments on how how can we incorporate obtaining data for these women along with the planning that we are going to do when we need to set up registries for surveillance during pregnancy? How hard is it to put these all together? Is it the same system, or is it -- does it have to be different?

DR. CHAMBERS: I think it's extremely simple to add to a pregnancy registry if you're doing follow- up anyway in the first year of life. And we work closely with Phil Anderson, (inaudible), and the -- in his estimation, if we can even collect the very basic information of how long the mother breastfed, whether she breastfed exclusively, and what medication she was -- if she continued to take the medication she was taking

during pregnancy and some very simple questions about any kind of difficulties that she noticed as the primary reporter, that's information that's lacking for most drugs during breastfeeding, and to do that as an additional small piece of a pregnancy registry, is, I think, a very important missing piece.

DR. DANA: I think it's easy in some settings and harder in others, so and I -- so, again, I'm thinking of our vaccine registries, where, you know, we get a spontaneous report of a woman who was inadvertently exposed to a vaccine, but we rarely get the reports of a woman who is lactating who was exposed to that vaccine.

So I think it depends on the setting, it depends on the medication how easy that is, because from the -- from our side -- from the spontaneous report side, I think it would be -- it's much harder to get that information in that setting because it's just not reported to us.

DR. GREENE: With -- Mike Greene. With respect to breastfeeding, one of the issues that

comes to my mind first was echoed from one of the speakers, from the open public speakers this morning, which is the disparate information that women get. And when it comes to breastfeeding, you've got an obstetrical care provider involved, whether that's an obstetrician or a midwife or a family practitioner. You've got the pediatrician. We have our nurses who are on the postpartum floor who all have an opinion. We have lactation consultants who have opinions. And they're often disparate. And, personally, I've frequently GOTTEN caught in the middle. Many of the patients I take care of do require medications during pregnancy and afterwards. And I'll go and look up in the AAP guidelines about breastfeeding for such-and-such a medication, and I'll -- the AAP will be fine with it, and I'll counsel the patient accordingly, and then the pediatrician will come in the next morning and say, "I don't care what that says. I don't want you breastfeeding on that medication."

So it's very difficult to get a

consistent message for patients, and ultimately I think we're going to need -- if you really want information about that, you really need to involve pediatricians, okay, because they're going to be the ones who are going to be taking care of the babies for the first year of their lives, and obviously beyond, but that's when the breastfeeding and formation is going to become apparent and relevant. But there's a tremendous about of disparate information that's imparted to recently delivered women with respect to breastfeeding.

DR. TASSINARI: So my sense is that everybody agrees that we should do it. Is anybody doing it now?

DR. CHAMBERS: Yeah, we collect information on breastfeeding, and in a project that we're just starting, we'll be proactively collecting that information. We've done it and published it on SSRIs, following up on the pregnancy registry. Yeah, I think it's completely doable, and I think that Michael's comment is so

true. I mean, talk about an orphan population. Women just don't know what to do and get -- and are -- because there's alternative, to formula feed, are put in a really difficult position.

DR. TASSINARI: And, Adrian, I'm wondering, is your challenge in collection something that can be -- I don't want to say be fixed, but can -- is this a change of just changing communication strategies in order to be able to be more successful in getting the data, or do you think there are other challenges there that are going to prevent you in the adverse spontaneous setting?

DR. DANA: So, again, I think we have a little bit better chance -- and, again, I'll be very honest with you. We collect, in our spontaneous registries, infant data up to two years afterwards. But our -- you know, while I have a somewhat better success rate at getting pregnancy outcomes, I only have a 30 percent loss to follow-up in our registries.

We have, actually, a great deal of

difficulty following those children, to be very honest, partly because it's a switch in provider, so now I've enrolled this provider, right, but now I have to get permission from the mom to enroll like the next provider. So it is difficult, and I actually don't know what you can do, because the spontaneous reports that we get are sent to us as an adverse event, so to speak, or somebody who's requesting information, and we grab them and enroll them, because it's been an exposure.

We get many fewer calls about exposures during lactation. So we'd have to think very carefully about how we could capture that information in a spontaneous way. If we did it in another prospective way, it might be different.

DR. TASSINARI: Any last comments or thoughts? On the phone? Well, with that, I think I will turn -- am I turning it over to Vicki or Solomon? Thank you very much, panel.

DR. IYASU: Well, this day and a half have been really terrific. It's really exceeded my expectations. We've heard a lot. And I think

we have a great assignment here for us at the FDA. I think we've heard themes. I'm not going to paraphrase all the things that we heard and all the pearls of wisdom that you've shared with us, but sort of in the -- in terms of the pregnancy registry and the discussions that we've had, I think one of the key things that came out is that, yes, they have provided some useful information, but they can get better, and there are things that we can do to make them relevant, to make them provide information that is key to the questions that women in general have in terms of childbearing, and also the medications that they might want to use for different conditions.

So one theme that came is that, yes, the partnership has to be built with the participants in the pregnancy registry; that they are key in terms of both as generating the information that will be used eventually, but as ultimately the ones who are going to be benefitting society from generating that knowledge. So we need to be making them central to that.

But also we heard that there's been good data from single product (ph) registry -- exposure (ph) registries, but I think the way the move is, for efficiency -- for also an ability to ask many different kinds of questions, need to be thinking more about how to move to (inaudible) registry, where we can see -- we can evaluate multiple exposures and also have internal control groups that would be more valid references for the comparisons that we might be making.

We also heard that we need to up the bar in terms of the kind of standards that we need -- we expect from this kind of efforts to understand medication risk during pregnancy. So it's a call, really, for FDA to come out with a guidance, but that guidance should not be limited just to how we do pregnancy registries or pregnancy exposure registries. It should also encompass other methodologies, other databases, other approaches.

And that's why we actually termed this workshop today -- we didn't call it this is about pregnancy registry only. I mean, if you look at

the title, it's really approaches about assessing medication safety, which means really not just pregnancy exposure registries.

But I think I want to share also, in terms of thinking about what we are trying to achieve by doing pregnancy registries or any other approach, when we're looking at risk, whether we are in -- you know, we may be in the different stages of developing a risk profile for medications. Sometimes we're talking about a signal duration effort. Where are we in that paradigm of trying to identify what the medication risks are when exposure has occurred during pregnancy?

So the signal detection and surveillance efforts necessarily have to be followed by some confirmation that those cases that generated the signal are actually real cases, real clinical cases. So that's probably one of the stages that need to be understood in the beginning.

And the next question might be how big is this risk? So the quantification of that risk

is really dependent on many different things. One of them is really how many exposed women might be in any particular database that you're looking at? So the quantification is a very relevant question, but also we have to really understand what I was trying to communicate based on what we find from that quantification. Are we really trying to understand whether there's a twofold increased risk, a threefold increased risk, or, as Allen said, is there some risk threshold that we're trying to exclude? So we need to be very careful and be very open about what we're trying -- what we're setting up to measure in this efforts.

And then the last effort, or maybe complementary with the quantification aspect, is characterizing that risk by different risk factors, by different demographic groups, or, you know, disease conditions. So there's a lot that you can do in terms of pinpointing and understanding safety by different parameters.

We also heard a lot about measuring medication safety during pregnancy is not just

about birth defects. There are a lot of other outcomes that are relevant and that could be measured, and so we need to be expanding sort of the outcome definitions that we have and the kind of outcomes we're interested in beyond the birth defects arena. And I think that's -- that came out loud and clear.

So we heard a lot about complementary methods today, and I think they hold a great promise, and there are many opportunities for us to leverage existing medical records, and there are great suggestions that we got from the panel today about what kind of things that we can do in terms of standardizing definitions, coding, and other things with medical -- with EMR data.

So I think those are things that are maybe not just FDA's purview, but I think this is sort of a bigger effort than just what FDA can do, so we'll be engaging with others as well in terms of trying to make them standardized. And I think we have had experience doing something of that nature with the Sentinel initiative, where there are

about 18 data partners, where the data actually put into a common data model, so -- using the same dictionary, the same approach, the same -- to the extent -- to -- in fact, sometimes even running the same kind of template programs to generate some data. So there is -- that -- we can leverage that experience into the pregnancy arena as well.

Then lastly what I want to touch upon, sort of this trade-off between validity and power. And I think that's a very important question, and it sort of goes back to the question that -- the comment I made about what I are we trying to measure, what are we trying to exclude? And it's more common for the FDA, when we're faced with a decision about safety, that we're often dealing with multiple data streams, multiple evidence streams, and not all of them may be saying the same thing.

It's great that when they all point to the same direction, but often we're faced with maybe different conflicting results. But then what comes into that picture assessment is really

the -- what -- how much reliable -- how reliable are the data from the different data streams? So this idea of what is the quality of the evidence, what weight should we actually assign to different sources of evidence that -- in making a decision about whether a medication is safe or not safe? And that's all done in the context of benefit/risk. And so it is not that easy, but, you know, we have to all be thinking about the quality of the data and the evidence that are generated and how much weight do we need to -- you know, do we give to the different data streams? And that's like a challenge for us and a challenge for everybody, because you could make only decisions based on the totality of the evidence, not just on one data stream only. That's why in clinical trials, for efficacy, we ask for complementary clinical trial, for example. So replication is really a very important aspect of some of the weighing of the assessment or of the data that we get from the different sources.

So we heard a lot also about FDA's role

in terms of the making sure that we have a guidance, that the guidance should be really more about not just considerations, but really telling us about best practices in -- whether you're doing a pregnancy exposure registry or you're using healthcare databases to assess medication safety.

And we heard a lot of advice also that says that it should really necessarily include, you know, how to use these complementary databases. They are not a replacement. And we often, you know, talk at the FDA that we don't just depend on one system. We depend on the evidence that's generated from multiple sources. We actually appreciate that there are multiple data sources, multiple evidence streams, but they don't always necessarily tell you the same thing. So that's where the weighing of the evidence -- and that -- you're using -- whether we're using (inaudible) or not comes into the picture.

Funding was something that a lot of you raised, and I think that is a critical question in the healthcare arena, now, where we have a lot of

competing sort of research arenas. For the FDA, of course, we're very much interested in what we can do in terms of generating more money or more funds for these kind of activities. And we partner with other federal agencies. We partner with the private sector. FDA's not a great source for funding, but whatever we have, you know, I think, you know, we've sort of made use of the little money that we have. I think a good example is probably the MEPREP effort, where the seed money was really to provide sort of some evidence of whether it's workable to actually have a system that links birth outcomes with the records, EMR data or electronic health record data of the mother.

So the proof of concept, it works, but then it comes to the question of can we scale it up, and scaling it up is going to require, really, a lot of discussions and leveraging the resources of multiple stakeholders. And so that's in -- that's where we are now, I think, in the middle of the discussions about how do we make this a

national resource so that it's not just FDA accessing the data, it's not just one group accessing the data. How do we make it accessible to all who are interested in working this?

So when we're talking about healthcare databases, it's really about making sure that we have access -- we have to have governance structure for the data. We have to have quality standards, not just for what goes into this databases, but what are the methodologies that are used to generate the information that's going to be actionable?

And also whether we can come up with specific standards for when we (inaudible) exposures, whether the kind of guidances that we need to have should really be targeted towards that specific environment or context in which medications are used.

So I think there's a lot of work that needs to be done. You've given us a lot of food for thought. But that calls for action. So we're going to be looking through all the transcripts

also that you -- you know, that will be generated from this meeting. It will be available also to you, so -- probably in about 30 days, as Vicki said. So we're working from the same sort of set of information that has been generated out of this incredibly useful and very important meeting. So I really want to thank every who participated in this. Particularly I wanted to thank the panel for your time, for your generous sharing of all your knowledge and experience. I want to also thank the presenters for the terrific presentations. I want to also thank the folks who actually stepped up and gave terrific comments during the open public comment period. And lastly, but not least, I want to thank the terrific FDA team that put together this meeting. You really did an incredible job, and I want to thank you for your efforts. And I think we have more work. And, Lynne, you want to say a few words? You okay? And I want to thank, you know, the leadership in FDA for supporting this effort. Lynne has been very instrumental in this. Layla

Sahin, who's been leading this effort. Kate Gelperin. I can't name everybody, but it's a number of people behind the scenes who have actually contributed to this, so thank you so much, and have a safe trip.

MS. MOYER: Does Office of Women's Health or CBER have any closing remarks they'd like to provide?

DR. SCOTT: Pam Scott, Office of Women's Health. I want to echo Solomon's thank you to all of you for taking time out of your busy schedule to spend two days with us to share your expertise and provide valuable feedback to all of us. We will be closely reviewing everything that you've said, and especially as it relates to the pregnancy registry Web page.

We will be taking your comments into consideration as we plan future updates and restructuring of the program registry listing. Thanks to you once again for coming out and sharing with us.

DR. NGUYEN: I think Solomon did a great job with closing up, so I'll let everyone go.

People are packing up, so I don't want to delay any further. Thank you.

MS. MOYER: Thank you, everyone.

(Whereupon, at 12:44 p.m., the meeting was adjourned.)

CERTIFICATE OF NOTARY PUBLIC

I, Chaz Bennett, the officer before whom the foregoing deposition was taken, do hereby certify that the witness whose testimony appears in the foregoing deposition was duly sworn by me; that the testimony of said witness was recorded by me and thereafter reduced to typewriting under my direction; that said deposition is a true record of the testimony given by said witness; that I am neither counsel for, related to, nor employed by any of the parties to the action in which this deposition was taken; and, further, that I am not a relative or employee of any counsel or attorney employed by the parties hereto, nor financially or otherwise interested in the outcome of this action.

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I, MARY E. YOUNG, hereby certify that I am not the Court Reporter who reported the following proceeding and that I have typed the transcript of this proceeding using the Court Reporter's notes and recordings. The foregoing/attached transcript is a true, correct, and complete transcription of said proceeding.

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