

Capital Reporting Company
Food and Drug Administration Public Meeting 05-29-2014

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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

Thursday, May 29, 2014

Food and Drug Administration

White Oak Campus

10903 New Hampshire Avenue

Building 31

Silver Spring, Maryland 20993

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1 P R O C E E D I N G S

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

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

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

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

4 The slide presentations for all of our
5 presenters will be posted on the FDA Web page with
6 the meeting announcement. Transcripts of the
7 meeting will be available approximately 30 days
8 after the meeting. You are encouraged to post
9 comments to the docket, which is open until June
10 30th, 2014, with your feedback.

11 Restrooms are outside of the main
12 conference room and in the back area of the lobby.
13 We will have one 15-minute break at approximately
14 20 minutes after 10 today, and that's the only
15 break, because we'll be adjourning at 1:15, so we
16 have a very busy and packed morning. The kiosks
17 in the lobby are open for refreshments during the
18 break.

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

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1 transcriptionist as well as the participants via
2 the webcast.

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

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

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

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

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

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

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1 Group at Merck.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

22 DR. MITCHELL: Allen Mitchell from the

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

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

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

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

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1 free makeover, you know, in our guidance document.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

1 mind that we can all get alert fatigue.

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

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

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

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

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

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

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

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

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

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

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

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

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

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1 needed data on outcomes in pregnancy was somewhat
2 heretical.

3 That was in 1991, and I remember because
4 I was about, oh, 36 weeks pregnant at the time.
5 Okay? And as I look back, I think about the fact
6 that I was pregnant with a young woman who is now
7 23 years old and assigned to her first submission,
8 and I think about what time has passed and really
9 how patience has paid off. Patience has paid off.

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

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

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

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

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

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

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

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

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

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

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

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1 that.

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

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

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

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

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

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

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

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1 pregnancy registry ideas.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

22 The finding, of course, lacks

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

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

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

1 that exposures to SSRIs in the second half of
2 pregnancy represented 3.7 percent in the cases and
3 0.7 percent in the controls, so the odds ratio --
4 the adjusted odds ratio was 6.1, with a lower
5 confidence bound of 2.2.

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

12 What gave us some confidence that this
13 finding had some validity was that we found no
14 increased risk for early-only exposure, and we
15 also found no increased risk for non-SSRI
16 antidepressants. So that paper was published -- if
17 I -- there we go -- with Tina as a first author,
18 and the rest of us -- she and Ken were very much
19 involved in the analysis, of course, and this was
20 a study published in the New England Journal in
21 2006 based on the case-control data.

22 I think it's important to point out that

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

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

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

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

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

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

8

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

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

1 practitioners used and worried about as well as
2 their patients.

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

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

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

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

5 OTIS, as you've heard, is a North
6 American- wide network of university and hospital-
7 based services, and it's been in existence since
8 1979. It provides service in terms of risk
9 counseling to 80 to 100,000 pregnant women and
10 providers, and they also have a very solid
11 research activity, which collaboratively, excuse
12 me, conducts prospective pregnancy registry
13 exposure cohort studies, with a track record
14 of productivity over 20 years and funding
15 from government and industry.

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

22 And here, just to highlight the outcomes

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

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

22 The maternal interviews and medical

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

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

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

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

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

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

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

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

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

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

18 DR. MITCHELL: I'm sorry?

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

21 DR. MITCHELL: Yep.

22 DR. STAFFA: Thanks.

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

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

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

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

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

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

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

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

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

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

4 The VAMPSS program is an established
5 public- private partnership. On the public side,
6 we have government participation on the advisory
7 committee, we have government funding. On the
8 private side, the professional organization is the
9 coordinator, the Quad AI, and we have professional
10 organization representatives on the advisory
11 committee and industry funding as non-voting
12 advisory committee members.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

17 MEPREP currently has linked infant and
18 mother data on women who delivered a live born
19 infant from January 1st, 2001 through December
20 31st, 2008 and the children born to these women.

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

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

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

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

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

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

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

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

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

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

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

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

22 In addition to all these files, which

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

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

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

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

1 live birth for the period -- for the year 2005.

2 And as you can see, the age distribution is
3 actually very similar for MEPREP as compared to
4 the U.S. population for a similar time period.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

7 So we had a medical chart review done by
8 a trained instructor, and also it was adjudicated
9 by physicians who had expertise in this field as
10 well, and then that way, we came to knowing
11 whether they were a confirmed case or not. I'll
12 talk more about that on the next few slides.

13 Sorry if this is a little small, but this is our
14 schematic diagram from our manuscript that we're
15 hoping to get published soon.

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

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

3 And then from that, you'll see here we
4 identified 10,000 mothers with sulfonamide
5 exposure during their first trimester, 63,000 of
6 the non- teratogenic antibacterials, and roughly
7 400,000 of the non-exposed mothers. We excluded
8 just under two and a half thousand mothers who had
9 both a sulfonamide and non-teratogenic
10 antibacterial.

11 So that left us with around 6,000 --
12 7,615 sulfonamide used during the first trimester.
13 Then we did the matching process from that, and we
14 ended up, and there was one excluded -- one infant
15 excluded because it had trisomy, after the chart
16 review was performed. And then we ended up with a
17 cohort of 7,614 sulfonamide users. So we had that
18 same amount in each of our two comparator groups
19 because they're matched one to one.

20 And then our final analyses, there were
21 some -- we ended up with 6,000 -- down here,
22 6,698, because we wanted to use everyone who had

1 complete data on all the covariates. Whoops.

2 So why did we use this study design?

3 Why not a typical case-control study? And as I
4 was just saying, we wanted to validate every
5 single birth defect in here. So if we had chosen
6 a case-control design where we had looked at all
7 the cases within our cohort, then if we have a 3
8 percent prevalence, roughly, out of the million
9 babies, you're looking at 30,000 cases. Even if
10 we drop it down to those who met our inclusion
11 criteria of around 500,000, you're looking at
12 15,000. And then even if you drop it down further
13 with only the 7,000 or drop that down half again,
14 you know, you're looking at 15,000 cases or so, or
15 7,000 cases.

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

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

4 What we ended up with was out of our
5 20,000 or so in our final cohort, we ended up with
6 provenance of around 4 percent of potential cases,
7 so we were close in the ballpark there. And these
8 two diagrams down on the bottom of this slide
9 here, they just show the difference. There's a
10 bit of trade-off here. Obviously, neither design
11 is the best design, but if you look at the left-
12 hand diagram, it's the typical case cohort study,
13 which is what we used.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

1 data are readily available at each site, so we can
2 run these studies very fast. And for future
3 studies, we can not only look at outcomes during
4 perinatal period, but also long-term follow-up.
5 Because this cohort now finished in 2008, it's now
6 2014, so we -- they may be six, seven years old,
7 the youngest ones in the cohort, so we could
8 follow them for that time period.

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

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

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

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

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

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

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

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

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

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1 at the actual raw data.

2 And lastly, MEPREP, it's an excellent
3 source of data for future research in this area.

4 And one more slide. Thank you. And this is a
5 joint slide from Susan as well, potential
6 development into full- scale program, looking at
7 different mechanisms and funding at the moment.
8 As Susan mentioned, there's a potential of linking
9 datasets to other external datasets: death
10 certificates, cancer registries, and also vital
11 signs, et cetera.

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

18 Thank you. That's all.

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

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

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

10 DR. STAFFA: Okay.

11 DR. COSTER: (Inaudible).

12 DR. STAFFA: Perfect.

13 DR. COSTER: So

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

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

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

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1 us off. Thank you.

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

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

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

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

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

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

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

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

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

18 This kind of shows you a little bit of
19 difference between the MHS population and the U.S.
20 population. You can see we're a little
21 bit young, and then you can also see that our
22 retirees are a little bit more robust than the

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

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

10 And then on that, I'm going to turn it
11 over, because we're short on time here, to Dr.
12 Conlin. And is somebody going to be advancing for
13 --

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

1 Next slide, please.

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

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

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

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

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

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1 neoplasms in infancy.

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

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

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

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

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

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

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

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

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

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1 Next.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

14 So the Mother-Child Database is housed
15 within the Pharmacovigilance Center and was
16 initially funded by the FDA from October 2009 to
17 2012. The primary goal of the funding was to
18 develop a mother- child database linking
19 pregnancies to birth and the other pregnancy
20 endpoints that would allow for rapid drug
21 assessment as well as feasibility of drug adverse
22 event associated with medication use before,

1 during, or after pregnancy.

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

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

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

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

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

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

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

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

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

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

13 So there are four major steps in
14 identifying pregnancies within PVDAS, and the
15 first thing that we did was to identify end of
16 pregnancy indicators and -- through a list of ICD-
17 9 and CPT code. And I will go over that a little
18 bit more detail as to how this occurs in our
19 system.

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

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

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

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

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

1 pregnancy care date using codes from pregnancy
2 care indicator list.

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

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

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

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

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

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

22 We also have some other -- some

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

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

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

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

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

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

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

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

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

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

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1 work or not work.

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

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

14 MS. MOYER: Seven --

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

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

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

4 DR. STAFFA: Thanks.

5 (Whereupon, a break was taken.)

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

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

16 DR. NALEWAY: Yes, I'm here.

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

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1 great. So go ahead, Dr. Naleway.

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

8 My disclosure statement, I have received
9 some research funding from GlaxoSmithKline. Next
10 slide, please. So this is just an overview of the
11 Vaccine Safety Datalink. It's a collaboration
12 between integrated care delivery systems and the
13 Centers for Disease Control, and the project's
14 been around since
15 1990.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

16 So we have done some validation work
17 with the algorithm. We identified close to
18 596,000 pregnancies that ended in 2002 through
19 2006. And the distribution of those pregnancies
20 is about 75 percent live births, 12 percent
21 spontaneous abortions, 9 percent elective
22 abortions, and 4 percent other outcomes, which is

1 really similar to national survey data for
2 pregnancy outcomes.

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

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

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

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

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

22 So that's just something to keep in

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

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

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

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

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

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

22 So after we figured out how to identify

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

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

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

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

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

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

22 So we now have a pregnancy covariate

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

19

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

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

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

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

22 And I wanted to talk about our goals.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

1 able to work this slide thing.

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

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

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

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

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

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

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

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

22 Pregnancy outcomes may have differing

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

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

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

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

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

22 DR. GELPERIN: Thanks, Judy. We will

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

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

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

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

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

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

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

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

1 medication in pregnancy, and typically physicians
2 extrapolate drug dosage regimen from non-pregnant
3 subjects or even men, which can lead to over- or
4 under-dosing and potentially fetal toxicities.

5 And this is due to many factors, and particularly
6 the lack of pharmacokinetic trials in pregnancy.

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

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

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

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

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

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

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

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

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

11 And, lastly, incentivize pharmacokinetic
12 and vaccine studies in pregnancy and lactation.

13 At the end, I would like to thank you for the
14 opportunity to present on behalf of Society for
15 Maternal-Fetal Medicine. Thank you.

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

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

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

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

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

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

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

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

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

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

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1 has not been mentioned once as a data source.

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

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

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

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

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

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

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

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

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

17 And this is a list just from the CDC,
18 which they published recently. If you look at the
19 12 most -- or 11 most used drugs -- and none of
20 them actually are what I would call new drugs for
21 which pharma is still investing a lot of money,
22 but these are the drugs that should concern us

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

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

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

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

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

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

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

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

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

10 DR. GELPERIN: Thank you, Dr. Dewulf.

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

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

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

22 The chapter on pregnancy registries in

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

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

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

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

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

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

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

12 So my thoughts today are really based on
13 20 years of experience and observations working in
14 vaccine safety, with the Vaccine Safety Datalink
15 at CDC and then in drug safety with the Sentinel
16 Initiative led by the FDA. Many of the challenges
17 that we're facing now are exactly the same,
18 remarkably similar, overlap with the challenges
19 that were faced by vaccine safety questions and
20 drug safety questions.

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

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

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

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

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

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

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

1 channel blocker usage associated with neonatal
2 seizures.

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

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

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

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

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

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

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

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

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

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1 health and well- being worldwide.

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

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

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

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

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

22 And, finally, the third paper, which was

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

6 So I think I'm out of time for my brief
7 example. I think my take-home message was just
8 that while randomized trials have studied a total
9 of 3,000 women with mild to moderate hypertension
10 in pregnancy, we could create a cohort now of
11 29,000 women at three health plans with rich blood
12 pressure data and medication data. And I think
13 these opportunities really are out there to be
14 explored, and there's huge potential here.

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

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

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

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

22 As rheumatologists, we realize that it's

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

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

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

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

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

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

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

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

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

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

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1 DR. STAFFA: Dr. Cragan?

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

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

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

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

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

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

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

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

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

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

12 DR. STAFFA: Dr. Mitchell?

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

4 DR. STAFFA: Thank you, Dr. Conlin.

5 Other burning, smoldering, clarifying questions?

6 Dr. Greene, another smoldering question?

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

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

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

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

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

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

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

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

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

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

9 DR. STAFFA: Other comments?

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

12 DR. MITCHELL: Well --

13 DR. STAFFA: Dr. Albano?

14 DR. MITCHELL: Oh.

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

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

6 DR. STAFFA: And Dr. Mitchell?

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

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1 satisfied by that arm's length relationship.

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

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

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1 time in my view.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

1 group.

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

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

20 DR. STAFFA: Dr. Greene?

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

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

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

22 And that same problem may be encountered

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

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

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

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

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

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

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

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

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

20 DR. STAFFA: Dr. Berliner?

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

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

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

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

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

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

14 DR. STAFFA: Dr. Coster?

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

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1 I know the Department of Defense feels that way.

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

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

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

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

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

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

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

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

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

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

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

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

22 And then they do -- they engage, on our

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

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

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

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

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

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

22 I think we should think of this as not

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

18 DR. TASSINARI: Do you have a second
19 one?

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

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

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

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

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

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

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

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

17 DR. TASSINARI: Thank you. Anybody else
18 ready to go? Trinkka?

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

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

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

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

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

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

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

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

22 And, you know, whether you centrally

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

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

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

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

7 DR. TASSINARI: Jan?

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

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

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

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

15 DR. TASSINARI: Yes, Craig?

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

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

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

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

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

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

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

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

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

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

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

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

3 DR. TASSINARI: Thank you. Adrian?

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

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

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

12 DR. TASSINARI: Thank you. Yes, Sonia?

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

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

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

17 DR. TASSINARI: Thank you. Elise?

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

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

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

21 DR. TASSINARI: Thank you. Diana?

22 MS. JOHNSON: Sure. I thought Julia had

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

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

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

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

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

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

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

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

9 DR. TASSINARI: Thank you. Peggy or
10 Ava?

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

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

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

7 MS. MOYER: Yeah.

8 DR. TASSINARI: -- connection.

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

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

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

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

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

9 DR. TASSINARI: Thank you.

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

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

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

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

6 DR. TASSINARI: Michael, any thoughts?

7 DR. NGUYEN: I don't at this point.

8 Thank you.

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

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

22 DR. TASSINARI: Very good. Well, I

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

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

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

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

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

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

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

1 consistent message for patients, and ultimately I
2 think we're going to need -- if you really want
3 information about that, you really need to involve
4 pediatricians, okay, because they're going to be
5 the ones who are going to be taking care of the
6 babies for the first year of their lives, and
7 obviously beyond, but that's when the
8 breastfeeding and formation is going to become
9 apparent and relevant. But there's a tremendous
10 amount of disparate information that's imparted to
11 recently delivered women with respect to
12 breastfeeding.

13 DR. TASSINARI: So my sense is that
14 everybody agrees that we should do it. Is anybody
15 doing it now?

16 DR. CHAMBERS: Yeah, we collect
17 information on breastfeeding, and in a project
18 that we're just starting, we'll be proactively
19 collecting that information. We've done it and
20 published it on SSRIs, following up on the
21 pregnancy registry. Yeah, I think it's completely
22 doable, and I think that Michael's comment is so

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1 true. I mean, talk about an orphan population.
2 Women just don't know what to do and get -- and
3 are -- because there's alternative, to formula
4 feed, are put in a really difficult position.

5 DR. TASSINARI: And, Adrian, I'm
6 wondering, is your challenge in collection
7 something that can be -- I don't want to say be
8 fixed, but can -- is this a change of just
9 changing communication strategies in order to be
10 able to be more successful in getting the data, or
11 do you think there are other challenges there that
12 are going to prevent you in the adverse
13 spontaneous setting?

14 DR. DANA: So, again, I think we have a
15 little bit better chance -- and, again, I'll be
16 very honest with you. We collect, in our
17 spontaneous registries, infant data up to two
18 years afterwards. But our -- you know, while I
19 have a somewhat better success rate at getting
20 pregnancy outcomes, I only have a 30 percent loss
21 to follow-up in our registries.

22 We have, actually, a great deal of

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1 difficulty following those children, to be very
2 honest, partly because it's a switch in provider,
3 so now I've enrolled this provider, right, but now
4 I have to get permission from the mom to enroll
5 like the next provider. So it is difficult, and I
6 actually don't know what you can do, because the
7 spontaneous reports that we get are sent to us as
8 an adverse event, so to speak, or somebody who's
9 requesting information, and we grab them and
10 enroll them, because it's been an exposure.

11 We get many fewer calls about exposures
12 during lactation. So we'd have to think very
13 carefully about how we could capture that
14 information in a spontaneous way. If we did it in
15 another prospective way, it might be different.

16 DR. TASSINARI: Any last comments or
17 thoughts? On the phone? Well, with that, I think
18 I will turn -- am I turning it over to Vicki or
19 Solomon? Thank you very much, panel.

20 DR. IYASU: Well, this day and a half
21 have been really terrific. It's really exceeded
22 my expectations. We've heard a lot. And I think

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1 we have a great assignment here for us at the FDA.
2 I think we've heard themes. I'm not going to
3 paraphrase all the things that we heard and all
4 the pearls of wisdom that you've shared with us,
5 but sort of in the -- in terms of the pregnancy
6 registry and the discussions that we've had, I
7 think one of the key things that came out is that,
8 yes, they have provided some useful information,
9 but they can get better, and there are things that
10 we can do to make them relevant, to make them
11 provide information that is key to the questions
12 that women in general have in terms of
13 childbearing, and also the medications that they
14 might want to use for different conditions.

15 So one theme that came is that, yes, the
16 partnership has to be built with the participants
17 in the pregnancy registry; that they are key in
18 terms of both as generating the information that
19 will be used eventually, but as ultimately the
20 ones who are going to be benefitting society from
21 generating that knowledge. So we need to be
22 making them central to that.

1 But also we heard that there's been good
2 data from single product (ph) registry -- exposure
3 (ph) registries, but I think the way the move is,
4 for efficiency -- for also an ability to ask many
5 different kinds of questions, need to be thinking
6 more about how to move to (inaudible) registry,
7 where we can see -- we can evaluate multiple
8 exposures and also have internal control groups
9 that would be more valid references for the
10 comparisons that we might be making.

11 We also heard that we need to up the bar
12 in terms of the kind of standards that we need --
13 we expect from this kind of efforts to understand
14 medication risk during pregnancy. So it's a call,
15 really, for FDA to come out with a guidance, but
16 that guidance should not be limited just to how we
17 do pregnancy registries or pregnancy exposure
18 registries. It should also encompass other
19 methodologies, other databases, other approaches.

20 And that's why we actually termed this
21 workshop today -- we didn't call it this is about
22 pregnancy registry only. I mean, if you look at

1 the title, it's really approaches about assessing
2 medication safety, which means really not just
3 pregnancy exposure registries.

4 But I think I want to share also, in
5 terms of thinking about what we are trying to
6 achieve by doing pregnancy registries or any other
7 approach, when we're looking at risk, whether we
8 are in -- you know, we may be in the different
9 stages of developing a risk profile for
10 medications. Sometimes we're talking about a
11 signal duration effort. Where are we in that
12 paradigm of trying to identify what the medication
13 risks are when exposure has occurred during
14 pregnancy?

15 So the signal detection and surveillance
16 efforts necessarily have to be followed by some
17 confirmation that those cases that generated the
18 signal are actually real cases, real clinical
19 cases. So that's probably one of the stages that
20 need to be understood in the beginning.

21 And the next question might be how big
22 is this risk? So the quantification of that risk

1 is really dependent on many different things. One
2 of them is really how many exposed women might be
3 in any particular database that you're looking at?
4 So the quantification is a very relevant question,
5 but also we have to really understand what I was
6 trying to communicate based on what we find from
7 that quantification. Are we really trying to
8 understand whether there's a twofold increased
9 risk, a threefold increased risk, or, as Allen
10 said, is there some risk threshold that we're
11 trying to exclude? So we need to be very careful
12 and be very open about what we're trying -- what
13 we're setting up to measure in this efforts.

14 And then the last effort, or maybe
15 complementary with the quantification aspect, is
16 characterizing that risk by different risk
17 factors, by different demographic groups, or, you
18 know, disease conditions. So there's a lot that
19 you can do in terms of pinpointing and
20 understanding safety by different parameters.

21 We also heard a lot about measuring
22 medication safety during pregnancy is not just

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1 about birth defects. There are a lot of other
2 outcomes that are relevant and that could be
3 measured, and so we need to be expanding sort of
4 the outcome definitions that we have and the kind
5 of outcomes we're interested in beyond the birth
6 defects arena. And I think that's -- that came
7 out loud and clear.

8 So we heard a lot about complementary
9 methods today, and I think they hold a great
10 promise, and there are many opportunities for us
11 to leverage existing medical records, and there
12 are great suggestions that we got from the panel
13 today about what kind of things that we can do in
14 terms of standardizing definitions, coding, and
15 other things with medical -- with EMR data.

16 So I think those are things that are
17 maybe not just FDA's purview, but I think this is
18 sort of a bigger effort than just what FDA can do,
19 so we'll be engaging with others as well in terms
20 of trying to make them standardized. And I think
21 we have had experience doing something of that
22 nature with the Sentinel initiative, where there
are

1 about 18 data partners, where the data actually
2 put into a common data model, so -- using the same
3 dictionary, the same approach, the same -- to the
4 extent -- to -- in fact, sometimes even running
5 the same kind of template programs to generate
6 some data. So there is -- that -- we can leverage
7 that experience into the pregnancy arena as well.

8 Then lastly what I want to touch upon,
9 sort of this trade-off between validity and power.
10 And I think that's a very important question, and
11 it sort of goes back to the question that -- the
12 comment I made about what I are we trying to
13 measure, what are we trying to exclude? And it's
14 more common for the FDA, when we're faced with a
15 decision about safety, that we're often dealing
16 with multiple data streams, multiple evidence
17 streams, and not all of them may be saying the
18 same thing.

19 It's great that when they all point to
20 the same direction, but often we're faced with
21 maybe different conflicting results. But then
22 what comes into that picture assessment is really

1 the -- what -- how much reliable -- how reliable
2 are the data from the different data streams? So
3 this idea of what is the quality of the evidence,
4 what weight should we actually assign to different
5 sources of evidence that -- in making a decision
6 about whether a medication is safe or not safe?
7 And that's all done in the context of
8 benefit/risk. And so it is not that easy, but,
9 you know, we have to all be thinking about the
10 quality of the data and the evidence that are
11 generated and how much weight do we need to -- you
12 know, do we give to the different data streams?
13 And that's like a challenge for us and a challenge
14 for everybody, because you could make only
15 decisions based on the totality of the evidence,
16 not just on one data stream only. That's why in
17 clinical trials, for efficacy, we ask for
18 complementary clinical trial, for example. So
19 replication is really a very important aspect of
20 some of the weighing of the assessment or of the
21 data that we get from the different sources.
22 So we heard a lot also about FDA's role

1 in terms of the making sure that we have a
2 guidance, that the guidance should be really more
3 about not just considerations, but really telling
4 us about best practices in -- whether you're doing
5 a pregnancy exposure registry or you're using
6 healthcare databases to assess medication safety.

7 And we heard a lot of advice also that
8 says that it should really necessarily include,
9 you know, how to use these complementary
10 databases. They are not a replacement. And we
11 often, you know, talk at the FDA that we don't
12 just depend on one system. We depend on the
13 evidence that's generated from multiple sources.
14 We actually appreciate that there are multiple
15 data sources, multiple evidence streams, but they
16 don't always necessarily tell you the same thing.
17 So that's where the weighing of the evidence --
18 and that -- you're using -- whether we're using
19 (inaudible) or not comes into the picture.

20 Funding was something that a lot of you
21 raised, and I think that is a critical question in
22 the healthcare arena, now, where we have a lot of

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1 competing sort of research arenas. For the FDA,
2 of course, we're very much interested in what we
3 can do in terms of generating more money or more
4 funds for these kind of activities. And we
5 partner with other federal agencies. We partner
6 with the private sector. FDA's not a great source
7 for funding, but whatever we have, you know, I
8 think, you know, we've sort of made use of the
9 little money that we have. I think a good example
10 is probably the MEPREP effort, where the seed
11 money was really to provide sort of some evidence
12 of whether it's workable to actually have a system
13 that links birth outcomes with the records, EMR
14 data or electronic health record data of the
15 mother.

16 So the proof of concept, it works, but
17 then it comes to the question of can we scale it
18 up, and scaling it up is going to require, really,
19 a lot of discussions and leveraging the resources
20 of multiple stakeholders. And so that's in --
21 that's where we are now, I think, in the middle of
22 the discussions about how do we make this a

1 national resource so that it's not just FDA
2 accessing the data, it's not just one group
3 accessing the data. How do we make it accessible
4 to all who are interested in working this?

5 So when we're talking about healthcare
6 databases, it's really about making sure that we
7 have access -- we have to have governance
8 structure for the data. We have to have quality
9 standards, not just for what goes into this
10 databases, but what are the methodologies that are
11 used to generate the information that's going to
12 be actionable?

13 And also whether we can come up with
14 specific standards for when we (inaudible)
15 exposures, whether the kind of guidances that we
16 need to have should really be targeted towards
17 that specific environment or context in which
18 medications are used.

19 So I think there's a lot of work that
20 needs to be done. You've given us a lot of food
21 for thought. But that calls for action. So we're
22 going to be looking through all the transcripts

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1 also that you -- you know, that will be generated
2 from this meeting. It will be available also to
3 you, so -- probably in about 30 days, as Vicki
4 said. So we're working from the same sort of set
5 of information that has been generated out of this
6 incredibly useful and very important meeting. So
7 I really want to thank every who participated in
8 this. Particularly I wanted to thank the panel
9 for your time, for your generous sharing of all
10 your knowledge and experience. I want to also
11 thank the presenters for the terrific
12 presentations. I want to also thank the folks who
13 actually stepped up and gave terrific comments
14 during the open public comment period. And
15 lastly, but not least, I want to thank the
16 terrific FDA team that put together this meeting.
17 You really did an incredible job, and I want to
18 thank you for your efforts. And I think we have
19 more work. And, Lynne, you want to say a few
20 words? You okay? And I want to thank, you know,
21 the leadership in FDA for supporting this effort.
22 Lynne has been very instrumental in this. Layla

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1 Sahin, who's been leading this effort. Kate
2 Gelperin. I can't name everybody, but it's a
3 number of people behind the scenes who have
4 actually contributed to this, so thank you so
5 much, and have a safe trip.

6 MS. MOYER: Does Office of Women's
7 Health or CBER have any closing remarks they'd
8 like to provide?

9 DR. SCOTT: Pam Scott, Office of Women's
10 Health. I want to echo Solomon's thank you to all
11 of you for taking time out of your busy schedule
12 to spend two days with us to share your expertise
13 and provide valuable feedback to all of us. We
14 will be closely reviewing everything that you've
15 said, and especially as it relates to the
16 pregnancy registry Web page.

17 We will be taking your comments into
18 consideration
19 as we plan future updates and restructuring of the
20 program registry listing. Thanks to you once
21 again for coming out and sharing with us.

22 DR. NGUYEN: I think Solomon did a great
job with closing up, so I'll let everyone go.

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1 People are packing up, so I don't want to delay
2 any further. Thank you.

3 MS. MOYER: Thank you, everyone.

4 (Whereupon, at 12:44 p.m., the
5 meeting was adjourned.)

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1 CERTIFICATE OF NOTARY PUBLIC

2 I, Chaz Bennett, the officer before whom the
3 foregoing deposition was taken, do hereby certify
4 that the witness whose testimony appears in the
5 foregoing deposition was duly sworn by me; that
6 the testimony of said witness was recorded by me
7 and thereafter reduced to typewriting under my
8 direction; that said deposition is a true record
9 of the testimony given by said witness; that I am
10 neither counsel for, related to, nor employed by
11 any of the parties to the action in which this
12 deposition was taken; and, further, that I am not
13 a relative or employee of any counsel or attorney
14 employed by the parties hereto, nor financially or
15 otherwise interested in the outcome of this
16 action.

17

18

19

— CHAZ BENNETT —
Notary Public in and for the
STATE OF MARYLAND

20

21

22

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1 CERTIFICATE OF TRANSCRIPTION

2

3 I, MARY E. YOUNG, hereby certify that I am not the
4 Court Reporter who reported the following
5 proceeding and that I have typed the transcript of
6 this proceeding using the Court Reporter's notes
7 and recordings. The foregoing/attached transcript
8 is a true, correct, and complete transcription of
9 said proceeding.

10

11

12

13

14

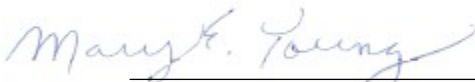
15

16

17

18

19 Date

— 
MARY E. YOUNG

20

21

22

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