FOOD AND DRUG ADMINISTRATION (FDA)

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

PUBLIC MEETING
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The Great Room, Room 1503
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A P P E A R A N C E S

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ELISE BERLINER, PhD
CHRISTINA CHAMBERS, PhD, MPH
AVA MARIE S. CONLIN, DO, MPH*
COL TRINKA COSTER
JANET CRAGAN, MD, MPH
MICHAEL F. GREENE, MD
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Industry Representatives:

ADEL ABOU-ALI, PharmD, ScD, MS
ADRIAN DANA, MD

A P P E A R A N C E S (Cont.)

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Appearing via telephone. * * * *

C O N T E N T S

C O N T E N T S (Cont.)

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P R O C E E D I N G S

WELCOME AND INTRODUCTION

MS. MOYER: My name is Vicki Moyer. And I serve as a regulatory project manager in the Center for Drug Evaluation and Research in the Office of New Drugs in the Pediatric and Maternal Health Staff.

On behalf of the Planning Committee, I welcome you to this public meeting to discuss study approaches and methods to evaluate the safety of drugs and biological products during pregnancy in the post-approval setting. Your attendance and participation today in person and via the webcast are sincerely appreciated. We would like to thank the many individuals inside and outside of FDA who have put a significant amount of time and effort into bringing this meeting to fruition.

Before we begin, I would like to share a few housekeeping details. Please silence your cell phones and Blackberries and other devices. Please check in at the tables outside the lobby if

you have not done so already. Agendas and discussion questions are available at the registration tables.

Open public comment speakers need to sign in at the speaker registration table. If you have not checked in at the meeting registration desk, you need to do so. Otherwise, you may not be able to speak during your time. If you have not registered in advance to speak and would like to speak, we will try to accommodate you if we have extra time. Alternatively, please submit your comments to the public docket.

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

Restrooms are outside of the main conference room in the back of the lobby area, towards the coffee kiosk. We will have a 15-

minute break at around 9:45 in the morning and also one around 3:20 in the afternoon. Lunch will be at noon. At the kiosks in the lobby, coffee and other refreshments are available for purchase during the breaks and lunch hour.

Before proceeding with our first speaker, I will provide the panel members with some instructions and ask them to introduce themselves. During the meeting, please remember to turn on and speak into the microphones every time the moderator recognizes you to speak and turn them off when you're not speaking. Clearly state your name each time before you speak since the meeting will be transcribed.

Now I would like to introduce Dr. Solomon Iyasu, who will be our first speaker.

MEETING OBJECTIVES AND GOALS

DR. IYASU: Good morning. It is my pleasure to welcome you on behalf of CDER and FDA to this public workshop, which is really a very important activity that we have been concerned about for some time. And so Dr. Kweder, who is

actually the deputy director, is running late. So maybe if she arrives in time, she might want to give some remarks. But for the purpose of the first introduction into this subject area, I just wanted to lay out sort of what the needs are and what we are gathered to do during the next day and a half.

So the topic for discussion today is "Study Approaches and Methods to Evaluate the Safety of Drugs and Biological Products During Pregnancy in the Post-Approval Setting." Okay. So why are we here, really? As you know, human data which is about medical product safety in pregnancy at time of market approval is really very scant, if not absent. So almost all the safety data that we collect or we get about human experience is really obtained in the post-approval period. Some of it is because there is intentional exposure because there are some conditions that require use during pregnancy. So we can't really avoid it. So we learn some -- we get some data from those exposures or they're really for approved uses in

terms of, let's say, vaccines, where the use might be indicated in pregnant women. So there are data that are collected post-marketing that could be useful, to understand, the safety profile of the medical product.

There is also unintentional exposure to products that happens in the post-market period. As you know, you know, about 50 percent of pregnancies are unplanned. So there has got to be unintentional and also accidental exposure to medical products during pregnancy, even before pregnancy is recognized.

So let me just go over a little bit of the history. I think, you know, the first guidance that FDA published on pregnancy registries was in 2002. In that guidance, we say that we could request studies, primarily pregnancy registries, of sponsors to understand the safety profile of drugs if we have a question that is of concern.

And generally there was voluntary participation by pregnant women into these

registries. We specified that they should be prospective so that outcomes are collected later on; that is, the data collection about exposures and other covariates should be done before the outcome of pregnancy is known -- so that's what we call prospective -- and that we should have a valid reference population or comparator group to compare it to.

So these are some of the main pillars of this pregnancy registry, the request that we have been issuing for several years. But things changed in 2007 under FDAAA, which is the legislation that provided FDA authority to require studies if we have this prior knowledge based on pharmacological chemical class or animal data or clinical trial data about a potential safety issue of a serious nature if a drug is used during pregnancy.

The other trigger might be that the product is indicated for use in pregnancy as vaccines or drugs for chronic conditions. And another possibility or reason or trigger for

requiring studies might be that there is a high likelihood of use in females that are of reproductive age such that inadvertent exposure during pregnancy may be expected. So in those conditions, FDA does have the authority to require studies to be conducted by sponsors.

Well, what has been our experience to date with pregnancy registries? I think we have had many pregnancy registries that have been implemented. There have been some successes. There have been some failures. So part of the focus of today's discussion will be really to collectively look over what our experience has been in terms of what has been successful, what have we gotten out of registries, how can they be improved. So the next talk after me actually will be an FDA presentation by Dr. Leyla Sahin and also Hoda Hammad, who would be talking about our experience from an exploratory analysis of experience of registries from the FDA context, sort of from our perspective.

We have not been really only restricted

to pregnancy registry. We have had some initiatives also to try to sort of expand our ability to address issues of pregnancy exposures and safety. And one of those programs is what we call Medication Exposure in Pregnancy Risk Evaluation Program, which is an attempt to link exposure data during pregnancy with outcomes, which means linking it to the birth certificate and other records. And so there would be actually a presentation about this experience also. I think it's the second day of our program.

And then there have been a number of other federal efforts as well. And I think there will be some talk that has been given about the other federal efforts, including the DOD. And also we will be looking at what opportunities there are using or leveraging such databases. There are also other approaches that will be discussed, which will be a focus, really, for the second day of the workshop, which is really talking about alternative methods beyond pregnancy registries, which is really an important activity.

I think there are a lot of data and opportunities that can be taken advantage of from really thinking about how we can make them better, how can we leverage those databases, the methodologies to really inform safety during pregnancy.

So, as I say, the main focus is really on pregnancy registry but allotting a whole half-day, really, on alternative methodologies beyond pregnancy registries. So those are the two areas. So we're trying to gather as much input and suggestions from a wide variety of folks here, including regulators, researchers, pharmaceutical industry, the public health agencies, health care providers and the public. So you really represent a wide spectrum of stakeholders today. And we're really eager to hear about your views and about the experiences about implementing pregnancy exposure registries with respect to really understanding the safety profile and medications and other products within pregnancy.

And then the second is really, as I say, alternative complementary approaches. I mean, we

are not saying that we are abandoning the whole effort of doing pregnancy registries but how can we really complement that effort with other methodologies and other databases?

So the meeting objectives are really to understand the current status of pregnancy exposure registries and identify successes and challenges and also identify strategies to improve the design and conduct of pregnancy registries so that, you know, we get the data that it will be important that would inform labeling, at least from a regulatory perspective but also provide information to patients and prescribers about rational use of medications during pregnancy.

We also want to get some ideas and input about best practices for outreach and communication about implementation of pregnancy registries. And that's an area that we're very concerned about. The fact that you have a pregnancy registry out there or maybe it's included in the label may not be enough. So what are the other ways of really doing some metrics so

that enrollment and retention and also success of conducting the registries become a reality?

Then the last is alternative post-marketing approaches for assessing medical product safety.

So today, really, a lot of the focus would be on pregnancy exposure registries and post-approval data, which will be really starting us off with a discussion about pregnancy registries. That will be the FDA presentation I talked about. And then the topic 1 presentation, followed by a panel discussion about pregnancy exposure registries' perspectives/challenges from the real world on data collection and analysis. And the speakers and the panel questions are in your package for that.

This will be followed by an open public comment. And then later in the afternoon, we will have a specific discussion about enrollment, retention, and communication regarding pregnancy registries.

Tomorrow will be topic 3 and topic 4. So we'll be focusing entirely in the morning about alternative approaches, which will be followed again by an open public comment. And then the last session will be really how to move forward because, after all, the discussions and the input and the recommendations will be the next steps that we need to embark on specifically about moving forward in the field so that we have, actually, a system or set of databases and approaches and methods that will be really advancing the science in this field. I think the passion is there among everybody who is working in this field, but I think we need to think beyond sort of just the passion and then say, "What are the ways that we can collaborate together? What are the ways that we can improve the systems? What are the ways that we can really inform patients and also prescribers about the safe and effective use of medications during pregnancy?"

Well, one thing that I need to emphasize is that at this meeting, we're not going to be

talking about specific products per se. So there will not be any product-specific discussions. It will be really about talking about how do we get the methods and data that are needed to inform this field and how can we improve the systems that we have beyond what we have been doing for the last 10 or 20 years.

So I would caution that there should not be any discussion about specific products or product-specific issues at this meeting. And I think that it would really make it very helpful to us that all of you actually participate. We are very eager to hear not just from the panelists here but also from the public who are present here. There is a lot of interest. There is a lot of passion in this area. So step up to the mike during the open public period. And, you know, we would like to hear your ideas. And we want to have an open, collaborative discussion. And at the end of the day, you know, FDA is going to take all of these ideas that have been generated and try to come up with sort of better strategies for

addressing this field.

So, without further ado, I am going to introduce the next speaker. Oh, Lynne, you are going to do some remarks? Okay. So Lynne Yao is going to come to the podium and give some remarks. And she is actually the director of the Pediatric and Maternal Health Staff at FDA. She is within CDER. So thank you for stepping up.

DR. YAO: Thanks, Dr. Iyasu.

OPENING REMARKS

DR. YAO: So I am pinch-hitting for Sandy Kweder, who is my boss. And, unfortunately, she is, we have just been told stuck with a flat tire. So we'll all keep our fingers crossed that Sandy can actually make it to work.

I really don't have any prepared remarks. And I am not going to try and explain what Sandy was going to say. But I do want to make sure that we had a chance to introduce our panelists and allow our panelists to introduce themselves to each other.

So why don't we go ahead and start where

we would like to start? How about on this edge of the horseshoe? If you could just speak into the mike? You can just hit that button. You have to turn it on and then turn it off. If you could just tell us who you are and where you are from, just a few comments about where you are from?

DR. DANA: Yes. Hello. Good morning. I am Adrian Dana. And I work for Merck. And I have been involved in product safety at Merck for the last ten years. I am a pediatrician by training and was in practice for many years before that. Thank you so much for having us here today. I think this is an important topic.

DR. ABOU-ALI: Good morning. My name is Adel Abou-Ali. I work for Sanofi Pasteur in Canada. I have been with Sanofi Pasteur for about six months right now. Before that, I worked for the FDA for about three months. And thanks for having us here.

DR. CRAGAN: I am Jan Cragan from the National Center on Birth Defects and Developmental Disabilities at CDC. We conduct birth defect

surveillance and research projects, including outcomes related to medication use in pregnancy.

DR. HANSEN: Good morning. My name is Craig Hansen. I am an epidemiologist. I am from Center for Health Research at Kaiser Permanente Georgia and also from the School of Pharmacy and Medical Sciences at the University of South Australia. Thank you.

DR. HOLMES: Good morning. I am Lewis Holmes. I am here as the Director of the North American AED Pregnancy Registry.

DR. ALBANO: Hello. I am Jessica Albano. I am the Senior Director of Epidemiology at INC Research. We conduct post-approval studies, including pregnancy registries.

COL COSTER: I am Trinka Coster from the Department of Army. I run the Pharmacovigilance Center for the Army, where we monitor medication use in prescribing practice for the Department of Defense and also have established a mother-child database.

DR. ANDRADE: Hi. My name is Susan

Andrade, an investigator at the Meyers Primary Care Institute and the HMO Research Network. And I have been involved with the Medication Exposure in Pregnancy Program for quite a number of years now. Thank you.

DR. CHAMBERS: I'm Tina Chambers. And I am at the University of California San Diego in the Department of Pediatrics. And I am an epidemiologist and work with the MotherToBaby OTIS Pregnancy Registries and the VAMPSS system.

DR. SCOTT: Hi. I am Pamela Scott. I am the Director of Research and Development for the Office of Women's Health. I am an epidemiologist and a statistician by training. I am the former lead for FDA's Medication Exposure in Risk Evaluation Program. Currently I am in the Office of Women's Health, where we maintain and manage the FDA pregnancy registry webpage and other pregnancy-related outreach activities.

DR. IYASU: Yes. My name is Solomon Iyasu. I am the Director of the Office of Pharmacovigiliance and Epidemiology in the Center

for Drugs.

DR. TASSINARI: Good morning. I am Melissa Tassinari. I am a senior clinical adviser in CDER, Office of New Drugs, the Pediatric and Maternal Health Staff.

MS. MOYER: Good morning. I am Vicki Moyer. I am the senior project manager in the Pediatric and Maternal Health Staff.

DR. NGUYEN: Good morning. I am Michael Nguyen. I am a pediatrician by training and the Acting Director for the Division of Epidemiology in CBER.

DR. SAHIN: Good morning. I am Leyla Sahin. I am a medical officer with the Pediatric and Maternal Health Staff in the Office of New Drugs in CDER. I practiced ob-gyn for 12 years before coming to the agency 6 years ago. Thank you.

DR. HERNANDEZ-DIAZ: Sonia Hernandez-Diaz, Associate Professor of Epidemiology at Harvard School of Public Health. And my research focuses on the safety of medication during

pregnancy.

DR. BERLINER: I am Elise Berliner from the Agency for Healthcare Research and Quality. I am the Director of the Technology Assessment Program. I work with the Medicare coverage group. And because of their interest in coverage with evidence development and registries, a bunch of years ago, they asked us what we could do to help advance the methods and science of registries. So we have now just published the third edition of the AHRQ handbook on the users' guide on registries. And the third edition actually has a chapter now on pregnancy registries. And we have also started the registry of patient registries.

DR. GREENE: I'm Mike Greene. I'm an obstetrician-gynecologist at Massachusetts General Hospital. I practice maternal/fetal medicine. I am Director of Obstetrics there.

MS. JOHNSON: I'm Diana Johnson. And I am a study manager for the OTIS pregnancy studies.

DR. MITCHELL: I'm Allen Mitchell, Director of the Slone Epidemiology Center at

Boston University and the PI on the Birth Defects Study and also part of the VAMPSS system.

DR. YAO: In addition, we have a few participants over the telephone who couldn't actually make it to our lovely White Oak campus this morning. And I would have Dr. Ava Marie Conlin. I think you're on the phone. Can you hear us? And could you say hello this morning?

DR. CONLIN: I am on the phone. Thank you so much for having me. It's quite early here in San Diego, California. My name is Ana Marie Conlin. I am a preventive medicine physician. And I am at the Naval Health Research Center, where we led the Department of Defense Birth and Infant Health Registry. I am also principal investigator for a smallpox vaccine in pregnancy registry and an anthrax vaccine in pregnancy registry.

DR. YAO: Great. And also on the telephone, we have Dr. Peggy Honein. Dr. Honein, can you hear us? And can you introduce yourself?

DR. HONEIN: Yes. This is Dr. Peggy Honein from the Centers for Disease Control Birth

Defects Branch. I'm an epidemiologist.

DR. YAO: Great. And lastly we have Dr. Alison Naleway, who won't be able to join us this morning, but we are hoping that she will be able to join us this afternoon.

So thank you all, panelists, for introducing yourselves. We are really excited about the next day and a half. And we think, we hope, and we expect, that we'll get much needed advice to help lead the way in terms of the next chapter in pregnancy exposure registries.

And, with that, I would like to introduce our first speaker of the morning, Dr. Leyla Sahin; as she has introduced herself, a medical officer and reviewer and on our staff at the Pediatric and Maternal Health Staff in CDER. Come on up, Leyla.

PREGNANCY REGISTRIES AND OTHER POST-APPROVAL STUDIES CURRENT STATUS AND FDA OBSERVATIONS

DR. SAHIN: Vicki, I might need some help over here. Oh, here we are. Okay. All

right. Good morning, everybody. Today's talk will include some background information, some information on the regulatory history of post-market data collection in pregnant women. We'll provide an update on the current status of pregnancy registries. We'll also present some results from an exploratory review of pregnancy registries that we recently conducted. Hoda Hammad, an ORISE fellow in the Office of Surveillance and Epidemiology, will start by presenting the methodology of the review. And then I will present a summary of preliminary results. And then I'll also mention some of our observations about the results and then close with some summary comments.

Because pregnant women are usually excluded from clinical trials of investigational products, at the time of approval of new drugs and biologics, there are often no human data to inform safety during pregnancy. Data collection in pregnant women is usually performed post-approval. And this is the focus of this public meeting. We

recognize the importance of collecting pharmacokinetic and efficacy data in pregnant women when appropriate, but these topics will not be discussed. Collecting lactation data is also important, but this will not be discussed either. Collecting safety data to inform use of drugs and biologics in pregnancy is an important public health issue, not only for FDA and regulated industry but also for researchers; other federal agencies; health care providers; professional organizations; and, of course, patients.

Here's a timeline of the regulatory history of post-market data collection in pregnant women. In 2002, in an effort to standardize industry's approach to post-market data collection in pregnant women, the agency published the pregnancy exposure registry guidance, which includes recommendations regarding the conduct and design of pregnancy registries. In 2007, passage of the FDA Amendments Act gave the agency enhanced authority to require safety labeling changes and post-marketing studies to evaluate a safety issue.

In 2008, the proposed and lactation labeling rule published, which when finalized will change the format and content of pregnancy and lactation labeling and eliminate the pregnancy letter categories. The final rule will also improve data collection in pregnant women as information on a pregnancy registry, if one exists, will be included in a prominent position in the pregnancy section of labeling.

So where are we in 2014? The pregnancy registry guidance is now over ten years old. And the agency is planning to make revisions. Input received at this public meeting along with public comments received will be considered in revising the guidance.

The current status of pregnancy exposure registries is that they are the most common type of post-approval study in pregnant women required or requested by the FDA as a post-marketing requirement or commitment issued at the time of approval or after approval if there is a safety issue that has been identified. However,

the agency has had a concern that pregnancy exposure registries often fail to provide useful information, usually due to low enrollment. Often these studies are open for several years with little accrual of patients.

As described in the pregnancy registry guidance, factors that may affect the successful implementation of a pregnancy registry include the prevalence of the disease in females of reproductive potential; usage of the drug after it has been approved for marketing; awareness about the registry on the part of health care providers and patients; and collaboration among those who conduct a registry in terms of expertise and involving experts in birth defects research, such as the CDC and others; collaboration in terms of resources and leveraging existing infrastructure and systems may also help with the successful implementation of a pregnancy registry.

In preparation for this public meeting, we conducted an exploratory review to evaluate pregnancy exposure registries and their ability to assess

safety of medical products in pregnancy and to describe the characteristics of pregnancy exposure registries that have provided clinically meaningful data and those that have not so that we could have a better understanding of where there is room for improvement and learn from the successes.

The study team members included epidemiologists and medical officers across CDER and CBER and across offices and divisions.

I will now turn it over to Hoda Hammad, an ORISE fellow in OSE, who will describe the methodology.

DR. HAMMAD: Thank you, Dr. Sahin. Good morning, everyone. My name is Hoda Hammad. And I am an ORISE fellow working with Dr. Sahin and the FDA study team on this project. I'll be describing the study methods we used for our exploratory analysis of selected pregnancy exposure registries.

In order to describe and evaluate current pregnancy registries and their ability to

assess safety of medical products when administered to pregnant women, we chose a selected sample based on the list of pregnancy registries on the FDA Office of Women's website. We considered the sample to be broadly representative, although not necessarily comprehensive, and that it includes a wide variety of pregnancy exposure registries. We extracted data from the website starting in January 2014 and evaluated 59 medical products in all. We did not do a systematic review of the disease-based registries for logistical reasons as some of these registries contained hundreds of medical products, but we do have medical products that were analyzed from a variety of disease-based registries.

Here you can see a screenshot of the Office of Women's Health website where we extracted the pregnancy registry data.

While it is difficult to ascertain with certainty whether particular study results or communication efforts have the desired effect of informing clinical practice, we looked at these

four outcomes or milestones and considered them to be potentially associated with registry effectiveness for the purpose of this analysis.

The first thing we looked for was if there was a labeling change where the registry results were included in the product insert. Once we collected more information about each medical product, we looked to see if there was a stated target enrollment and if the stated target enrollment was achieved. We also looked to see if there were any references to data from the registry in clinical practice guidelines or if there were any publication of registry results in peer-reviewed journals.

In order to determine if any of the pregnancy registries had the outcome measures we were looking for, we conducted an extensive search of internal FDA databases. This included any protocols, reports, final study reports, or clinical reviews by FDA staff. We also looked at approved product labeling on the Drugs@FDA website to determine the history of product

labeling changes regarding safety of exposure during pregnancy. After that, we looked for any drug safety communications on the FDA Drug Safety Communications website. We also searched through electronic bibliographic sources to identify if there are any peer-reviewed publications which describe pregnancy registry results or if any provided recommendations for clinical practice or if other study methods were conducted by other researchers.

For data analysis, we used descriptive statistics to describe key features and characteristics we are interested in, including frequency counts and proportions. We stratified the data several different ways, including whether the registry resulted in labeling changes that were included in approved product labeling, whether the registry results were published in a peer-reviewed journal or peer-reviewed articles, and whether the registry reached target enrollments. Extensive quality assurance checks were also conducted by the core data analysis team

to ensure accuracy and completeness of the data for the key fields, which were specified for analysis. All the analyses were performed using SAS version 9.3.

So some of the registry characteristics we chose to focus on included time period of initiation of the registry, if it was started before or after the FDA guidance was published in 2002 or if it was started before or after FDAAA took effect in 2007. We also looked at if the indication for use of the medical product evaluated in the registry was a rare disease; if the registry included one medical product or multiple medical products; if it was implemented as a post-marketing requirement, a post-marketing commitment, or neither; if it was required under a risk evaluation and mitigation strategy, REMS; or whether the information about enrolling in the registry was included in the approved labeling; and if the registry includes patients from the United States only or from other countries.

Now I will turn the podium back to Dr. Sahin, who will describe some of the results of our analysis. Thank you.

DR. SAHIN: Thank you, Hoda.

Fifty-nine products from 38 pregnancy registries were evaluated, consisting mostly of drugs, followed by biologics and then vaccines.

The proportion of registries that were a PMR or PMC was pretty similar to the proportion of registries that were not a regulatory obligation. Seventy-six percent of products have registry enrollment information included in approved labeling. Fifty-three percent of products have registries that are U.S.-based only.

The duration of the registry was less than 5 years in 41 percent of the products, 5 to 10 years in 39 percent, and greater than 10 years in 20 percent.

In terms of pregnancy registry data that contributed to a labeling change, there were seven products. And these included Truvada, tenofovir/emtricitabine, based on data from the

Antiretroviral Pregnancy Registry; bupropion based on data from the Bupropion Pregnancy Registry; Singulair, montelukast, based on data from the pregnancy registry of the same name; Varivax, Proquad, and Zostavax vaccines based on data from the Pregnancy Registry for Varicella Zoster Virus-Containing Vaccines; and Mycophenolate based on data from the National Transplant Pregnancy Registry.

Here is an example of approved labeling informed by pregnancy registry data. This is from December of 2013. As we wait for the final Pregnancy and Lactation Labeling Rule to go through clearance and publish as a final rule, we have been encouraging companies to submit labeling in the new format. And here you can see the three new sections which consist of the risk summary, clinical considerations, and data. Data from the international Bupropion Pregnancy Registry are presented under the data section.

Here is another example of approved labeling informed by pregnancy registry data. And

this is from 2012. This is also in the new format. As you can see, the pregnancy registry information is presented first. And the data from the Antiretroviral Pregnancy Registry are presented at the bottom of the slide.

For the seven products with registry data added to approved labeling, results were also published in a peer-reviewed journal for six. Overall, for the total 59 products, interim or final registry results were published in a peer-reviewed journal for 22.

Pregnancy registry data for the following seven products contributed to clinical practice guidelines: Humira, adalimumab, based on data from the Organization of Teratology Information Specialists, OTIS, Autoimmune Diseases Study; Gardasil, Human Papillomavirus Quadrivalent Vaccine, based on data from its pregnancy registry; Viread, tenofovir, and Truvada based on data from the Antiretroviral Pregnancy Registry; Varivax, Proquad, and Zostavax Vaccine based on data from the Pregnancy Registry for Varicella

Zoster Virus-Containing Vaccines.

In terms of target enrollment, 22 of 59 products had a target enrollment stated in the protocol. And of these, three achieved a target enrollment.

In terms of registry status, 71 percent of products are still part of an ongoing registry. Seventeen percent are closed for feasibility reasons, most commonly due to low enrollment. And 12 percent are closed and considered completed.

Information about loss to follow-up of the registry's pregnancy outcome data was available for 32 of the 59 products. After excluding registries with low enrollment(less than 20 patients), the loss to follow-up rate was calculated for the remaining 21 products, with a median loss to follow-up rate of 23.4 percent, with a range of 1.6 to 52.7 percent and an interquartile range of 3 percent to 36 percent.

Some alternative approaches that were identified during the review that either contributed to labeling, were conducted or funded

by industry, or published in the literature include case control studies, cohort studies, claims database studies, case series and reports, European national birth register data, passive surveillance, enhanced pharmacovigilance, and inadvertent exposures during product development.

Some of the limitations of this exploratory review are listed on this slide. It did not include a systematic review of the six disease-based registries listed on the Office of Women's Health webpage, although some products from some of these registries were included in the review.

It is not a comprehensive review of all pregnancy registries. It did not assess pregnancy registry data quality or methodology or other factors that may contribute to the successful conduct of a registry, such as resources, expertise, etcetera. It also did not assess factors that affect the decision to add pregnancy registry data to labeling.

So what does all of this mean? The

exploratory review suggests that pregnancy registries have contributed safety data for use in labeling and clinical guidelines and also published in the medical literature. However, there is room for improvement. And there is a need to develop strategies to improve the conduct of pregnancy registries. And we look forward to hearing from the panel about this.

We are unable to draw conclusions using this exploratory study on characteristics that result in a successful registry. Study methods and sources of data other than pregnancy registries also contributed to informing risk.

In summary, pregnancy exposure registries by themselves may not be sufficient to collect data that inform product labeling. And we need to explore complementary study methods, which will be discussed tomorrow. Our goal is to improve health outcomes for pregnant women. And data collection in pregnant women is a shared responsibility among all stakeholders.

Thank you for your attention. And I

would be happy to take questions.

MS. MOYER: Does anyone on the panel have questions for Leyla or Hoda or Solomon?

DR. SAHIN: Yes? Go ahead, Michael.

CLARIFYING QUESTIONS FOR THE PRESENTERS

FROM THE PANEL

DR. GREENE: I would like to just make an observation about the criteria that you used for the impact of the registries. One of them was whether the registry met their criterion for enrollment for the size of the registry. In some cases, some of the registries' activities are to publicize the fact that these drugs should not be used during pregnancy. And the fact that fewer and fewer women have been exposed to the drugs actually may be a mark of the success of the registry in that they don't meet their criteria for enrollment because the word has gotten out that the drug shouldn't be used during pregnancy.

DR. SAHIN: Thank you. Thank you for your comment. Yes? I agree with your comment,

Dr. Greene. Thank you.

DR. TASSINARI: I think the challenge is going to be, though, how do we capture that because, you know, I think it is one of the points that we have to have suspected, but I don't know that we have documented it.

DR. GREENE: It's a little bit like knowing when the dog didn't bark.

MS. MOYERS: Any questions on the phone?

DR. TASSINARI: No lights are on. Very good.

TOPIC 1: PREGNANCY REGISTRIES - PERSPECTIVES/CHALLENGES RELATING TO DATA COLLECTION AND ANALYSES

MODERATOR INTRODUCTION TO TOPIC 1

DR. TASSINARI: Well, I guess, then, what we shall do is move into our first topic. We have a series of presentations this morning that we hope will provide us some information to look a little more closely at where we are today with the pregnancy exposure registries and how the different perspectives for data collection have

served us. I think Leyla has given you a little bit of a preview of where this is going, but we have specifically asked for some presentations to try and round out our perspectives on the current status of our data collection methods, particularly with pregnancy exposure registries.

So, with that, we would like to start with our first presentation. Dr. Sonia Hernandez-Diaz is going to speak to us about study design and methodology. Sonia?

STUDY DESIGN AND METHODOLOGY

DR. HERNANDEZ-DIAZ: Hi. Good morning. Thank you for inviting me to be here today.

As a disclosure, I have consulted for some pregnancy registries as an adviser. And I am the epidemiologist for the Anti-Epileptic Pregnancy Registry with Dr. Lew Holmes.

What I am going to do is to first give you an introduction to study designs, just a brief roadmap of some of the designs we are going to see in these next two days. And then I am going to focus on some specific methodological aspects for

pregnancy registries, including validity and efficiency, or power, aspects.

So, as an introduction, following an instructor that I learned from, Dr. Allen Mitchell, we can look at study designs for safety during pregnancy in two groups. One is in premarketing preapproval. We have some toxicological studies that are useful for us, but for teratogenicity and other effects in the fetus and in children as well they are usually poor predictors. We also have animal studies, but because of the variation of teratogenicity among different species sometimes are poor predictors for humans as well. And we have some clinical trials that typically exclude pregnant women. And that can take us to a whole different interesting discussion about the ethics of that.

So for pregnancy information, we are left with the post-approval studies. And there are some clinical trials. Some large trials might include, mainly inadvertently, some pregnancy women. And they can provide some information, but they

typically provide information on a handful of pregnant women. So they are not enough. So we can have them post-approval, some case reports or case series, sometimes under some surveillance systems. But they can both provide true signals but also often provide false alarms or no clues about something going on.

We have ecological studies that can look at geographical differences or trends over time. And these trends are typically explained by other things going on at the same time. So they are not ideal either.

So we are left with non-experimental, epidemiologic, studies for our research. And there we can see both cohort studies and case control studies. Within the cohort studies, some of them have been designed specifically to study birth defects, like the Collaborative Perinatal Project. But this huge cohort even, the Collaborative Perinatal Project, with over 52,000 women, when you want to look at a specific medication and specific defects, they have a small

sample size, or insufficient sample size. So most commonly what we do now is to have specific cohorts exposed to specific medications of interest. And those are the pregnancy registries that we are going to discuss this morning; for example, the OTIS pregnancy registries.

Then we have sources of four studies that were not designed specifically to do research or to study birth defects. There you probably have seen data coming from automated claims databases, such as Medicaid or HMO networks; computerized medical records, like the CPRD in the U.K. or here Kaiser Permanente; or pooling projects that combine these resources. And we are going to hear about MEPREP tomorrow.

For case control studies, we have some that are specifically designed to study one defect, but, more commonly, we have been using data from case control surveillance systems, like the Slone Epidemiology Center Birth Defect Study or the CDC-based NBDPS Study.

But I am going to focus on pregnancy

registries. And the definition of pregnancy registries is observational prospective cohort of women receiving a medication of interest as part of their routine clinical care who are enrolled during gestation before the outcome can be known. And then they are followed during pregnancy or even after pregnancy to obtain information on some outcomes. And then to evaluate whether that frequency is as expected or higher than expected, we compare them to a valid reference group.

As Dr. Iyasu has mentioned, the FDA has some guidelines for when these registries should be conducted. Right now it's when pregnant women are likely to be exposed or even women of childbearing age are likely to be exposed or when we believe there may be a potential risk; for example, vaccine. And there are some recommendations as well regarding when to enroll. And FDA has recommended that we want to enroll women after exposure but before the pregnancy outcome is known. However, if women enroll later, they are also typically enrolled in the

registries. But it is recommended that we look at them separately, at least in a sensitivity or secondary analysis.

As a result, there are many pregnancy registries. The website has been also mentioned already. And I am going to use one specific registry for my example because, as I mentioned, I work with Dr. Lew Holmes, the principal investigator of the North American Anti-Epileptic Drug Pregnancy Registry. And I am going to briefly go through the methods. Dr. Holmes is going to talk about it more in a little bit.

The registry was established at the Massachusetts General Hospital in Boston, 1997. It enrolls pregnant women exposed or using anticonvulsants/anti-epileptic drugs, as well as a reference group of friends and family members that are pregnant but not exposed to anticonvulsants. Women call, enroll, and then the registry obtains the consent. And then outcomes are validated with medical records.

Information is obtained through three

interviews: one at the enrollment, one at seven months gestation, and one around two months postpartum. And the interviews ask questions on anticonvulsants as well as some demographic, the indication, epilepsy or others, vitamin use, smoking, et cetera. And for every anticonvulsant reported, detailed information is obtained on those and on timing of use.

The registry considers two groups. The pure prospective refers to women who enroll before they had a prenatal test. And the so-called traditional prospective refers to participants who have enrolled after having had an informative test, like amniocentesis, chorionic villus sample, et cetera.

So I am going to go and focus on the methodological points. Dr. Holmes will talk more about the selection of comparison groups. I am going to discuss the issues pertaining to the enrollment in the registries.

In a typical registry, you can worry about women having pregnancy losses or ending

pregnancy at different times. If you were assessing, for example, prematurity. And those programs are important and affect not only pregnancy registries but any study evaluating birth defects. If you are missing terminations or miscarriages, then we are concerned about the potential implications, but where I am going to focus is on what is called in epidemiology left truncation, meaning that it's the time of enrollment where we can also have women enrolling at different times. And that's what these lines represent. The course represents just women that may be exposed to different medications or exposed and unexposed, being from the reference group. So this is data from the registry, just a random sample.

And here we have women enrolling around the second or third month of pregnancy typically, but there are some that are enrolling a little bit later. You have to remember that women have to recognize they are pregnant, go through their neurologist, and then be referred to the registry

or sometimes they find information on the website. So, as a result, we have women enrolling at different times.

What can be the implications of that? So the answer is that it depends on what you want to study. We will all agree that if we were studying infertility or problems with contraception, we would have to enroll women before pregnancy. Otherwise, if we were to enroll pregnant women, we could not study effects on fertility.

So the same thing for pregnancy losses or miscarriages. If that's the aim of the study, we cannot enroll women at 20 weeks of pregnancy because by definition, they didn't have miscarriage.

And what about when we are interested in the health of the offspring, often major malformations? If that's the case, if the outcome of interest is birth defects, then because we currently believe that the ecologically relevant period is the first trimester, we have to make sure that we enroll women ideally before the first

trimester. What would happen if we don't do that? Keep inKeeo in mind that when you are doing a registry, what would you expect to find if subjects are enrolled late in pregnancy, after prenatal screening and you have subjects to enroll and she had already a pregnancy test and there is a problem, a potential problem, with the fetus? Well, if there is a diagnosis and you include the women in the registry, you may be overestimating the risks because perhaps women after having a diagnosis will tend to look for information on enrolling in the registry.

However, you have a call from a woman and she had a diagnosis and you exclude these women that call with a diagnosis. You will be selecting a cohort in your registry without problems. So by enrolling after prenatal screening, at least for some defects, you may have to live with this situation.

And what about this other related problem? You have groups of exposed, and then you have a reference group. What would you expect to

find if exposed subjects are enrolled during the first trimester or before the prenatal screening but the unexposed group is enrolled after, later in pregnancy? And these graphs try to represent that situation. In red here, we have the exposed women, exposed to your medication of interest. And then you have the reference group of unexposed. If ideally all of them were enrolled in the registry at conception, then some of them will have, some pregnancies will have, an infant with a birth defect that we can sometimes diagnose early on. Sometimes we will not diagnose until delivery.

But keep in mind now that in the unexposed group, women were to enroll later. Then we could argue that those women who had diagnosis and perhaps even a termination and you ask them to volunteer for a registry that is not about a medication they are taking, they may not be in the mood to enroll in the pregnancy registry if they had a termination. If that is the case, then, as a result, you will be selecting women

preferentially without a birth defect. This is the theory. Now let me show you some real data from the North American Anti-Epileptic Drug Pregnancy Registry.

This graph here represents the enrollment time in gestational age at enrollment for women who call the registry and were on anticonvulsants/anti-epileptic medications, here the dark lines.

Just as an example, I was also providing just specifically that the distribution of enrollment time for two of the anticonvulsants, lamotrigine and valproic acid, just to give you an example. And, as you can see, there are no differences when we look at the specific drugs. However, in the unexposed groups of friends and family members, they tend to enroll a little bit later, which also makes sense. For you to invite a family member or a friend to enroll in the registry where you already enrolled, you have to know that she is pregnant and know easily. Unless this person is very close to you, that might take

some weeks. So that's not an unexpected situation.

Then, just for this presentation, we look at data for spontaneous abortion, even when that is not one of the main outcomes for the registry, but sometimes companies are required to present data on spontaneous abortion.

So we found that overall in all anticonvulsants, 353 out of 7,000 exposed had miscarriages and among the nonusers a much lower risk: 6/581. If you use good, simple, unconditional logistic regression without considering time at enrollment, that would be a fivefold increased risk. If we take into account when women were enrolled and compare women that were enrolled at the same time at the trimester level, the relative risk will go down to 2.7; if we go to the Greek level, a twofold increased risk. If we were to use a summary incidence rates ratio, as you know, the risk of miscarriage changes over time. So if we use this person time, we will have a similar result of twofold versus

fivefold.

If we were to restrict these women to prescreening and raise only prescreen for birth defects, the results will not change, as you would expect. So what happens with major malformations? An unconditional not considering time at enrollment, a relative risk for anticonvulsants overall will give a threefold increase risk. If we condition on the time and enrollment, the results will not change. However, if we take into account for malformations who enrolled before the screening, the relative risks do go down to twofold with wide confidence intervals. But it's still supporting that there may be a difference for defects overall if you don't pay attention to the prescreening and post-screen.

So, in summary, in this registry and I think in most registries, you will have enrollment that spanned throughout the entire pregnancy. And it may be different for the exposed and the reference groups. And in our case, it wasn't different for the specific medications.

If you are going to analyze spontaneous abortions or any other early event, your results may be sensitive to gestational age at enrollment. To analyze major malformations, your results may be sensitive to whether the women had prenatal screens before enrollment. Therefore, to minimize the left truncation, we will recommend to enroll women, of course, as soon as possible in pregnancy.

If you were studying outcomes such as spontaneous abortions, where the incidence is changing over time, you will have to consider that your exposed and reference groups have comparable time at enrollment. When the events may influence enrollment, like some specific birth defects, through the prenatal screening, the primary analysis must include only subjects enrolled before this event.

And now I'm going to move on to a few comments on power. Again, if the main outcome of interest is birth defects, then we are dealing with an outcome that overall has a prevalence at

birth of around two to three percent. If we want to focus on specific malformations, then we are talking about prevalences of 1 every 1,000 for the most common ones, like some cardiac or oral clefts.

If we do a power calculation, just to have an idea, and we try to focus on specific birth defects, for a relative risk of 20-fold, here we are talking about something close to Thalidomide for a huge increased risk. If we were to enroll 150 exposed in a registry and, say, double the number of unexposed, for a total number of subjects in our cohort of 450, then we will have sufficient power. For a 12-fold increased risk, again, like a very strong risk but not quite as 20-fold, we will double that number. For something closer to reality for a strong, a fivefold, increased risk in the risk of this specific malformation, we are talking about 1,500 or more exposed in our registry.

And this power calculation is a mathematical calculation. And, as you can see, if

you expect 1 out of every 1,000 births affected and we said that we had 300 in the exposed, this calculation allows for you to have a .3 of a person with a birth defect. So it's not reality but just to give you an example.

And, to give you a more real example, I am going to present data again from the North America Pregnancy Registry to give you an example of our experience with lamotrigine. And this table represents the sample size enrolled on lamotrigine in the registry divided into 100, 100 more. Then we have 200. And so far now the registry has a sample size for lamotrigine of over 1,800. So when the registry started collecting information on lamotrigine in 1997 or a little bit after when lamotrigine was being commonly used, for the first 100 women enrolled in lamotrigine, there were 2 with oral clefts. That's 20 percent. If you compare that with the expected 1 per 1,000, it's huge. And if you were conducting a registry and you had this huge risk, what could you do? It can be real; right? So you wait a little bit

more. You have 200 in oral cleft. That's 15 every 100, rather than 1 every 1,000.

But then you continue. And some years you have none. And at the end, when you have a larger sample size, now the cumulative risk is 3.9 per 1,000. It's still elevated but not quite as a 200-fold increased risk. And this graph represents what you would see in terms of here in the red lines the risk or the number of cases divided by the number of pregnancies enrolled on lamotrigine, the first 100, and then the second 100 enrolled. And now it is when we have over 1,700.

As you can see, at the beginning, with 2 cases in the first 100, the risk was 2 per 100, rather than 1 per 1,000, so a huge increased risk but with very wide confidence intervals. As data is accumulated, the risk went down. And the confidence intervals now are much narrower.

So I think that's a lesson learned and it is not to publish too early. Of course, at that time, we didn't know if it was going to go up or

down. But it's a lesson learned in terms of how small numbers can play games.

So, in conclusion, to end my presentation, let me review briefly the main advantages and disadvantages of pregnancy registries. They are prospective drug exposure studies. Therefore, there is no concern with recall bias. The information is typically collected before the outcome.

By concentrating on selected medications, you can increase efficiency versus doing pregnancy cohorts overall and particularly when you are studying uncommon drugs in relation to relatively common events. They are longitudinal. Therefore, you can present not only relative risk but also risk differences. You can interview moms and, therefore, get not only prescriptions but also real intake of the pills. You can study multiple exposures if you want to enroll multiple drugs in your registry and multiple outcomes, but those advantages come with some limitations. Some registries may not be

representative of the population in the sense that you may have volunteers or women exposed to specific medications; therefore, having a specific indication. So that population may not be representative or comparable to the general population.

Some registries lack a control group and may rely on an external comparison group that may or may not be comparable to them. Even when I said they are efficient because they focus on medication, still they cost time and, therefore, money. They have, most of them, a short follow-up. And if you are interested in late development, they may not provide that information. They have losses to follow-up. And you have to pay attention to the potential selective under-ascertainment. And they have limited powers for specific birth defects, as we show.

So those were my slides. Thank you very much.

DR. TASSINARI: Thank you.

(Applause.)

DR. TASSINARI: We have a few moments. We're running a little bit ahead. If anybody has a clarifying question, we can take those. Yes?

DR. BERLINER: Can you talk a little bit more about the enrollment? So it sounds like not all doctors are inviting patients to enroll and that some patients are finding the registry on their own. So could you talk a little bit more about how that is actually happening? Like what percent of doctors are actually asking patients to enroll? What percent of patients are accepting enrollment? How many patients are finding it on their own?

DR. HERNANDEZ-DIAZ: Yes. Dr. Holmes is the PI of the study. So he may want to go over that. I'll leave it up to him. But the registry is advertising in the labels. There are posters and information cards sent to neurologists, epidemiologists, and other clinicians that we sometimes contact through our presence in meetings. And I don't have the number right here.

I can look it up for you, the exact proportion of how many women who are calling because they were searching the web -- and that's certainly very common -- and find the registry and call versus those that are encouraged by their prescriber, clinician to enroll, which I know that happens, too, but I don't have the specific proportion of that.

And, again, maybe Dr. Holmes wants to comment on that. But the registry has spent efforts in this marketing of the registry to get to women through different methods.

DR. TASSINARI: I am glad you raised it. And we are going to be bringing that up again this afternoon after lunch because we specifically see that as an issue to have some further discussion. Yes?

DR. GREENE: Sonia, given the example that you just presented, what advice would you give or guidance would you give about when is the time to publicize a newly recognized apparent association?

DR. HERNANDEZ-DIAZ: Yes. That's a very good question. I don't know if I have the answer. I have been wondering myself. In part, I think it may be a topic to discuss when we discuss communication because, on one hand, you want to I think report what you have for others to replicate and for women to have information. And even when you may have a huge confidence interval, still that may be more information than nothing. However, in this case, depending on how you communicate and how the information is understood, that's why I think it is a communication issue. You can create alarms unnecessarily.

So I would say that if there is a way to communicate without anybody running away with a relative risk and saying, "20-fold increased risk," I would do it. I just still think that somehow it has to be public, at least for peers to go and try to replicate in their other resources. But, you know, it's hard to prevent them. There needs to be on the following day with a 20-fold increased risk. So it's a little bit dangerous.

And if we find a way to communicate these kinds of preliminary numbers with a lot of uncertainty and lack of information around it, that would be great.

DR. TASSINARI: I'd like to come back to that question when we have the larger panel discussion because I think there's much to be had there. Great.

If there are no other clarifying questions, I would like to invite Dr. Lewis Holmes for his presentation on comparison groups.

DR. HOLMES: Thank you very much for inviting me.

COMPARISON GROUP

DR. HOLMES: As you can see, Sonia and I work both on the same pregnancy registry. We have developed our slides separately and then compared them after mine had been submitted. And you will see that we have got some similar ones, but we're using them to make different points. I am really going to focus on the issue of the comparison group that we have recruited and I think is a good

model for the FDA to consider as it supervises pregnancy registries.

I think the point to make in describing what a pregnancy registry is, is that everyone needs to remember that it is not a clinical trial. We have a lot of requests for terminology and whatnot in a lot of our agreements that show that a lot of folks still can't get their heads around what a pregnancy registry is, but it's not a clinical trial. There are many variables in a pregnancy registry. And this is a list of several of those.

We're focusing today, my comments, on the last two items here: the inclusion and exclusion criteria, which are a crucial part of your comparison group; and then the actual comparison group itself.

As Sonia has pointed out, there are several steps in our process of enrolling a woman. We enroll among women who are pregnant throughout the United States and Canada. And the key issue here is at the end of the interview, the research assistant who is talking to the woman and using a

computer-assisted telephone interview tells her about our desire to have her help us recruit individuals who are also pregnant who are not taking these medications. So it is a verbal invitation at the end of the interview. And that is the essential beginning of the recruitment process.

So you have as you advise individuals about pregnancy registries the two models. To me, there are a lot of problems with the historical comparison group. I am going to focus on the internal comparison group. This is a system that Caitlin Reilly Smith, who is our project manager, developed early on several years ago. And now 10 percent of our enrollees each month -- we enroll about 50 women each month, and about 10 percent of them have continued to be women who are in the comparison group. And, as Sonia mentioned, they are friends and family members of the enrolled woman.

First, there is the issue of the number. And then there will be the issue of the specific

qualities of the malformation itself. One of my complaints to people is of the frequency of birth defects at birth is not three to five percent, as a lot of people are taught, or two to four percent, as Sonia showed in her slide. It really depends on your definition of a malformation, how you got the information, what your exclusion criteria are. I'll show you later the details of our exclusion criteria, but the gist of it is let's start with two studies we have done where we examined the children ourselves. And you can see we carried out a cohort study. Unfortunately, there is a typo in the year, but it was 2001 that it was published.

These were infants born to women taking anticonvulsant drugs at any of five hospitals in the Boston area. We examined the children ourselves with a protocol that makes you pay attention to details and be consistent and a rather boring thing to do. And the examiner was masked as to which children was born to a woman on the drugs versus a woman who was not on the

medication. You can see the rate was 1.8 percent.

Using a different approach, a malformation surveillance program, which we conducted at Brigham and Women's Hospital for 40 years, here is some data that has been published. You can see that using the pediatricians' findings, not our own exams, the rate was 2.24 percent.

If you subtract chromosome abnormalities and dominant/recessive disorders, it gets down to roughly two percent. And you can see one publication from several years ago. And the more complete data set is being analyzed right now.

Okay. Those are two of our studies showing roughly a two percent rate. These are other sources. They don't all give details on the inclusion and exclusion criteria, but you can see that there are four different major sources. Two are currently active. For example, the important Metropolitan Atlanta Congenital Birth Defects Program, MACDP, you can see there is a rate of 2.1 percent at birth. It was in the paper published

in 2007. The other one that's currently underway is Eurocat, which is a European registry-based system. You can see they have 2.3 percent; 2 of their older studies, similar outcomes.

My point is if you are talking about structural abnormalities with surgical, medical, or biological importance, the rate at birth is roughly about two percent. And then you would subtract the chromosome abnormalities and the recognized genetic conditions. And you would actually get slightly below that. So that is sort of step number one. If you have at the FDA a company submitting a proposal and it says the rate in the general population at birth is two to four percent, you should say, "Where did you get that four percent?" Usually they have no idea of where they got it, but they should have an internal comparison group that would be the basis for that rate.

These are the exclusions that we have used for all our studies for these 40 years. And they're published in the paper that is listed

there at the bottom. Anybody who examines babies knows that lots of babies have a lot of little diddly things that the mother may notice and may want you to discuss, but they are of no great significance biologically. These are extremely common. The study that is cited there from Birth Defects Research A showed that the frequency of these minor malformations is 20 times greater than the frequency of actual malformations.

Now let's get into the dynamics of specific findings. This is not where we are focusing on the rate, but you are actually saying you are looking at the reports that come in from the pediatricians, you are talking to the mother. She is saying the child has polydactyly. Well, everybody who does pediatrics and genetics knows that there's polydactyly and then there's polydactyly. And so you really need to be specific.

Think of how many pregnancy registries where you have seen as the outcomes the publication just says, "Polydactyly." Well, I

listed four here. And you can see number one, postaxial polydactyly, type b, extremely common. One in 100 African American infants has that, 1 in 1,000 Caucasian infants, extremely common, is not known to be associated with any exposure during pregnancy. And in our system, it would be excluded as an hereditary finding.

Then you see the other three types. The one that is probably most notable is to talk about the preaxial polydactyly, "preaxial" meaning, of course, the thumb side, as opposed to postaxial, the fifth finger side. My point is you can't just list polydactyly. There needs to be someone who knows birth defects, who has seen them before, who is not sitting there Googling the finding to make the comment on the quality or significance of that information.

Prematurity-related findings. These have become in the time since we started in 1997 an extremely common issue to wrestle with and develop your criteria for including and excluding a finding. Fortunately, a lot of prematurely born

infants are now surviving. Imaging is powerful. These children have imaging studies over and over and over during the time they are in the hospital before they go home. It is very common for an infant who is 28 weeks gestation to be found to have, as this slide shows, a patent ductus as well as a patent foramen ovale.

These are normal physiological findings. They are not a birth defect. And, yet, when people rely on ICD-9 codes, these are going to be listed by the poor, hardworking coder as a birth defect. One is a PDA. And the other is classified as a type of atrial septal defect. My point is you should be making a qualitative judgment on this story and using exclusion criteria that would consider the prematurity issue.

Probably the more contentious issue that we wrestle with all the time and people debate when we present our findings is, what do you do about findings during pregnancy by prenatal ultrasound? That technology has become extremely

common, but there is no systematic screening done among the women who enroll in our registry and, for that matter, among women in general. It's lot of variation from site to site in terms of the quality of the equipment, when the ultrasound screening is done, who is reading it, and so forth.

So we have always maintained that if the pediatrician doesn't find something at birth, it doesn't count. Others argue with that, which is their prerogative. And if they have an internal comparison group, they can certainly include them in both the exposed and the unexposed. And it will all balance out.

We found when we have followed up on the cases we have actually been told about a significant number of them go away and turn out not to be significant. So that would be an issue to bear in mind.

If you were high bound and determined to include things found by ultrasound, such as hydronephrosis, here is what our analysis showed

the effect would be. This is an analysis that Marie-Noel Westgate and I did of 1,000 consecutive births at Brigham and Women's Hospital, where we went through the medical record, Marie-Noel did, identified all of the diddlies that were recorded by the pediatricians, the birthmarks, the minor anomalies, and so forth, as well as the findings reported by the mother. If you insisted on including the ultrasound-only findings, primarily hydronephrosis, you would essentially add to your baseline rate two percent. So, in other words, if the baseline rate were two percent without ultrasound, you add the ultrasound only. Suddenly your baseline is four percent. And, as I said, if that's what you want to do and you do that in both your exposed and your unexposed comparison group, it all balances out and you have no problem. But if you are trying to use an historical record as a basis for your comparison group, how do you know which of those were detected during pregnancy?

One of the issues that is a fact of life for a pregnancy registry is how long are you going

to be funded? When we have started, we were supported only by companies. And that is still the case. And when we have findings, this is an issue related to Mike's question about, when do you publish? If you are not sure how long you are going to be funded, you might as well if you have a significant finding have the uncertainty a part of your decision-making in terms of okay Let's go ahead and publish this because we're not sure we're going to be around when the sample size is twice as big.

You can see from this other power calculation table, which Sonia also did for us, that yes, we have now enrolled almost 600 unexposed in the comparison group, but you can see that to have 80 percent power, just looking at changes in the overall 2 percent frequency of birth defects, we still need to go further to have 875. And you can see that if you try to get to changes in the frequency of cleft lip and palate, which, of course, the lamotrigine exposure example puts on the table, you really need thousands of

enrollees.

And so one of my take-home messages for you is pregnancy registries need to be designed to continue until you are able to speak to the frequency of specific malformations, not all malformations. And the only way you are going to do that is if you have funding that continues long enough to have thousands of enrollees. We have now enrolled over 9,000 women, for example.

This is our comparison group. At the time, there were 544 recruited. You can see these are the malformations that are listed. If you are one who likes the historical controls, I challenge you to find this listed in any of the lists of abnormalities in those tabulations. Some of these are very common findings in the general population. You can see one of the points here that I haven't talked about but is a major issue, septal defects are found in great frequency in all the imaging that newborns have these days. And you have to decide what size parameters you are going to use. We exclude the muscular VSDs because they are

extremely common and most of them go away. And we only include atrial septal defects if they have a certain size measurement. And, obviously, that is something that every registry has to decide separately.

Now, who are the women who refer them, and who are the women who enroll as the comparison group? This is a slide Sonia made for me. You can see that she has listed in the middle the women who are taking the seizure medication who refer their friends. And so here are their friends on the left. And the women who referred them are in the middle. And then here is the lamotrigine comparison group on the right side.

A pregnancy registry can make no pretense of enrolling a wide spectrum of society. Look here. Post-college education, significant number of these people. The folks who sign up for a pregnancy registry are not a random sample of society, no way to get around that. That is the reality.

Likewise, that means that they are not

going to be people with significant exposures to things that we know they shouldn't be doing. So for cigarette smoking, very small rate of smoking a pack or more a day. The same is true for alcohol use.

But if you bought at the FDA the manufacturer's preference for saying four percent is a normal rate of occurrence of birth defects, look what you would see. For the carbamazepine-exposed pregnancies, which is considered a teratogenic exposure, although of modest severity, that would just ride right under that four percent, would not be detected. Obviously valproate would stand out, but valproate stands out in every analysis you do in anticonvulsant drugs.

And here Sonia has shown this. And so you can see that our challenge for the women who are being enrolled who are friends and family members is to get them to enroll earlier. Right now we haven't been stressing that, but we hope among the advocates for this registry, the

obstetricians and the neurologists, who are a predominant source of referrals, that we can include in their message to the woman, "Please do it soon, rather than waiting until after you have had any prenatal screening."

So, in summary, I think if you are going to have a pregnancy registry, you really need to spend some time talking about what you are going to include and exclude before you get started. You need to have on your team someone who knows what these abnormalities are. We have a pediatrician sitting here. And there are plenty of pediatricians and neonatologists that could be very important contributors to a pregnancy registry, instead of, as I mentioned, the system our research assistants often use. They will Google something because they have no idea what it is. And you don't want that to be the basis for deciding whether something counts or not.

You need I think the unexposed comparison group, where you have the same staff, the same interviews, the same process. You are

encouraging the woman to sign the form so we could get the copies of the records when the woman says, "We saw the orthopedist last week," that you can get her to help you get the results from the orthopedist's exam, so forth. And then ultimately, of course, you need to have someone as skilled as Sonia who can do the analyses where you subdivide by the women who enroll before they have had prenatal screening versus the women who enroll after that.

So, in summary, these are the folks who do all of the work for us and would just emphasize the importance of the FDA considering the possibility of encouraging more vigorously the unexposed comparison group as a component of any registry going forward.

Thank you.

(Applause.)

DR. TASSINARI: Time for some clarifying questions. Any from the panel?

DR. SAHIN: Dr. Holmes, could you talk about the governance structure of the North

American Anti-Epileptic Drug Registry, please?

DR. HOLMES: Sure. We have been very fortunate in having a scientific advisory committee that has remained very much constant since we began in 1997. And so what we have done, initially meeting twice a year, now once a year, with these folks -- and Jan, to my right, Jan Cragan from CDC, is a member. Two neurologists; an obstetrician; epidemiologist; and a woman from the epilepsy program at NIH constitute the six people. We meet and go over our findings. We are meeting, actually, this coming Monday. We go through the state of the registry, what is happening, what we found. We go through the marketing. We get the answer to Elise's question about how many women signed up this year on the internet versus how many were referred by the obstetrician versus referred by the neurologists and so forth.

And then we, particularly in the beginning, presented questions of when do we publish this finding. And initially we referred

to medications by number so that when we discussed them with the scientific advisers, they just knew it as drug number 3, drug number 5, or whatever. And we made the decision to release it. And then they learned that the first drug we released was Phenobarbital. And we asked them to guess what we were releasing. And, of course, they were all over the place but had no idea that it was Phenobarbital. And then the second drug whose findings we released was drug number 5. And that turned out to be valproate. So we have gone through that process early on.

Then we had a moment of having to decide what we do with the new drugs where the risk for malformations is more subtle. And that is where the lamotrigine issue came up. And we had the decision to make about whether to release the findings when the first 700 had been enrolled and we had this dramatic increase in the frequency of oral clefts. And the group made the decision that we should go ahead and publish that, and we did. And anybody who is familiar with this literature

knows that it has been debated a lot ever since that came out and you saw in Sonia's slide that the rate has dropped steadily. And we predict that it's ultimately once you get up to three or four thousand enrollees, you will get down to a point that is probably going to be higher than the general population rate but not nearly as scary as that initial figure was.

So it's been us talking to them, showing them our findings, what do you think, this is what we think we should do. The good news is it has been a steady source of advice, very little turnover in the group. And that has worked. It was particularly important in the early years, when we were debating about when to release something. It is not nearly as much of an issue now. I mean, Sonia showed you a very sophisticated study that she and some of her colleagues at the School of Public Health have done on enrollment. This is the kind of finding that is very sophisticated and very interesting, but it's not something that the scientific

advisory committee is going to agonize about. It's just going to be fascinating to see it documented. But early on, it was, do we release? Do we run the risk of scaring people? Do we wait?

And so, you know, for a pregnancy registry with a limited funding, you don't pay these people. We don't pay the women who enroll. And so you're depending on the goodwill of colleagues who are interested in a topic and are willing to come to Boston for a day each -- well, it used to be twice a year, now once a year, to go over the findings. And we are grateful to them for having done that for so long because that has really made it work.

You can imagine another model where you would be paying folks thousands of dollars and so forth, but that just is not a realistic part of a pregnancy registry budget. But that is how it has worked. We meet separately and then we end that discussion and decide what we want to discuss with the representatives of the sponsors. And then the sponsors are invited in, their representatives,

usually one or occasionally two for each company. And so we and the representatives for the sponsors go over what we think is ready for prime time to talk about.

And when we publish something, we send around the manuscript to the sponsors a month before we submit it so they have a chance to give us their comments, questions, whatever with the understanding that we will consider whatever they say, but we necessarily won't change anything based on what they say.

And that has been another thing that has evolved since 1997. Initially a lot of the sponsors were very opposed to the idea of separate meetings, where we only met with the scientific advisers, and the people writing the checks were not in the room. But gradually over time, they became more comfortable with that.

And now our biggest question is, will the support continue? And we don't have any way to know whether it will or not, but you can see that if you are beginning to talk about specific

malformations, you have got to continue. I mean, a registry stops after 500 enrollees. You're not even to first base. And, you know, that's the big unanswered question. Will the companies feel the importance of continuing so we can begin to talk about heart defects and oral clefts and spina bifida and et cetera because I think that's where these registries should go if the exposure is common enough and the enrollment is at high enough rate?

DR. DANA: Hello. It's Adrian Dana. I had a clarifying question about the communication. And, you know, you say you decide to communicate. You know, I think that the communicating negative results in this setting is just as important to exposed women as communicating, you know, positive results of a defect that you are concerned about. And so, you know, what we have done in the past is we just communicate on a periodic basis. You know, if we had something that needed to be communicated more emergently, we would. And so I wondered, do you communicate on a yearly basis? Do

you put together some kind of a report or do you only communicate when you have a concern?

DR. HOLMES: One of the references in my slides was Sonia was the first author of the paper that appeared in Neurology in 2012. And that was the 11 drugs which had been taken as monotherapy by at least 50 enrolled women. And so among those 11, you have 2 or 3 good news stories, reassurance that this drug, that drug was not associated with a significant increase. So we have done both. But we have not had a systematic -- we haven't had a routine.

The Australian Anti-Epileptic Drug Pregnancy Registry is one that does what you were asking about. They every year publish wherever they are, what their results are. So the groups have done it different ways.

DR. TASSINARI: We will take one more question, and then we will head to break.

DR. NGUYEN: Dr. Holmes, do you think that your friends and family strategy for a comparator group is generalizable to other

products, like vaccines?

DR. HOLMES: I think it is the sort of thing that people need to look at and think about. For us, it has worked. And I think the value of an internal comparison group is really powerful. And so it would be interesting to hear the people who have worked on vaccines to comment on that.

But you need to get away from the idea that -- using historical comparison groups and get your own comparison group so you've got your own things that happen to real people, real time. So that's my plus side, but I would be interested to know what they think about using it.

DR. TASSINARI: Well, thank you. We have reached our break time. Okay. Go ahead.

MS. MOYERS: Just one housekeeping announcement for the invited panelists who let us know they would like to participate in the buffet lunch. If you could just please pay at the kiosk? If you have any questions, Paul Tran is at the registration desk. That is for the invited panelists. Thank you.

DR. TASSINARI: We will resume at 10:00 o'clock.

(Off the record.)

(On the record.)

DR. TASSINARI: Well, I think we will begin with our next presentation. We have two more presentations this morning. And then we have set aside some time to address a few questions that we have for the panelists related to the information that we have been listening to this morning.

So, with that, I'd like to ask Dr. Albano, how is from INC Research, to present on multi-product registries. Thank you.

MULTI-PRODUCT REGISTRIES

DR. ALBANO: Good morning. I am pleased to have the opportunity to speak to you all today and to share some of our experience with multi-product registries.

I wanted to begin by just reviewing a few of the important points that have already been brought up this morning: first, that most

information on the safety or risk of drugs related to pregnancy is collected after the drug has been approved and is used in pregnant women in the real-world setting. Pregnancy registries are generally implemented when there is either a safety concern, an indication for use during pregnancy, or a high likelihood of use in women of reproductive age. The purpose of pregnancy exposure registries is to provide human data on the safety risk profile of pharmaceutical products during pregnancy. In order to fulfill the goal of informing the decisions of patients and health care providers, it is imperative to initiate the registry as soon as possible using the most effective design strategy.

The objectives of this presentation are to differentiate single versus multi-product or disease-based registries; to demonstrate the appropriate use of each with examples; to discuss advantages, challenges, and special considerations; and to delineate some of the perceived barriers to implementation. The first

distinction to be made is between a product and a disease registry. In a product registry, the eligible population is identified based on exposure to a particular drug, biologic, or medical device, although the latter is of less relevance with regard to pregnancy registries. In a disease registry, the eligible population is identified by a common condition or diagnosis. Individuals may be treated or untreated. And among those treated, their therapy may include one or several different drug products. So while the product and disease registries have some distinct methodological differences, both have the potential to result in either a single or a multi-product registry. We will be discussing them together in the overall framework of multi-product registries.

As the term implies, a single product registry monitors a single drug or biologic product. There may be multiple formulations, varying doses, or different routes of administration as well as both brand and unbranded

versions. Single product registries are most appropriate for newly approved products, the first product in a new drug class, when there is a new indication for a marketed product, when there is a high likelihood for use in pregnant women of reproductive age, when the product is approved for use in a unique population, when the product has a known pregnancy or fetal risk, and when there is excess risk for a product compared to other treatment options.

As an example of a registry for a product with a known safety risk, the Ribavirin Pregnancy Registry monitors fetal exposures to brand and generic versions of products with a ribavirin component that are marketed in the United States. In contrast, the Adenovirus Vaccine Pregnancy Registry was designed to monitor outcomes of fetal exposure to adenovirus vaccine in the U.S. military, a unique population with a large number of reproductive age women.

In a simple scenario, a multi-product registry monitors multiple different products for

the same indication from a single pharmaceutical company. This type of registry is appropriate when the products are within a single drug class, have a similar risk profile, or are likely to be used in the same patient population. This type of registry may also be appropriate when concomitant exposures are of concern or when a combined registry is operationally and logistically feasible.

Each of these registries monitors pregnancy's exposures to multiple drugs used to treat the same condition or disease. The Sumatriptan, Naratriptan, and Treximet Pregnancy Registry includes three drugs indicated for the treatment of migraines. The MotHER Pregnancy Registry has expanded to include three HER2+ breast cancer treatments.

In the complex scenario, multi-product or disease-based registries monitor all of the marketed products used to treat a particular disease in a given region. This type of registry is appropriate when the products are manufactured

in combination, there are complex multi-drug treatment regimens, there is a high likelihood of polytherapy, there are frequent and new product approvals, internal comparisons are desirable, or when confounding disease or population characteristics may exist.

Two examples of long-term registries are the North American Anti-Epileptic Drug Pregnancy Registry and the Antiviral Pregnancy Registry. You have already heard quite a bit about the North American Registry, which monitors approximately 38 drug products used individually as monotherapy or as complementary polytherapy. The APR monitors approximately 30 single drug and 8 combination drug products. Twenty-five are indicated for HIV. Two are indicated for both HIV and hepatitis B. And three are indicated for hepatitis B alone.

I'm going to go into a few of the results from the Antiretroviral Pregnancy Registry. The registry began as a single drug registry in 1989 and has expanded over the past nearly 25 years to become a multi-product, multi-

sponsor registry. Through July of 2013, there have been almost 18,500 prospective cases enrolled from 67 countries. Seventy-eight percent of the reports in the registry are from the U.S. and its territories, and 9 and a half percent of enrollments have been lost to follow-up. Among the 38 drugs being monitored, there are currently 23 participating manufacturers.

Through July of 2013, there have been more than 16,300 prospective reports with outcome. Approximately half, or 48 percent, of pregnancies have exposure in the first trimester. Thirty-nine percent were initially exposed in the second trimester. And 13 percent were exposed beginning in the third trimester.

Among the 16,589 outcomes, there were 15,451 live births and 445 defect cases. The overall prevalence of birth defects was 2.9 percent. The 95 percent confidence interval ranges from 2.6 to 3.2 percent. The APR uses a comparison group primarily of the MACDP, which from 1989 to 2003 has a birth defect prevalence of

2.72 percent.

Among first trimester exposures, the prevalence of birth defects was 2.9 with a 95 percent confidence interval from 2.5 to 3.3 percent. This is compared internally by later trimesters, in the second and third trimester, but the risk of defects is not significant. The risk is 1.02.

In addition to evaluating drugs in aggregate and by class of antiretroviral therapy, they are analyzed individually when sufficient numbers of exposures have accumulated to warrant a separate analysis. The APR uses a threshold of 200 first trimester exposed cases. To date, there has been no concern among the individual drugs analyzed with the exception of two drugs, nelfinavir and didanosine, which have a modest but statistically significant elevated risk overall compared to the MACDP. However, there is no discernible pattern among the specific defects that had been reported.

Our Advisory Committee reviews in

aggregate and individual cases on a semiannual basis and as part of our published annual and semiannual reports provides a consensus statement that is there, a cumulative and comprehensive review of the data. I will summarize it by saying that the Antiretroviral Pregnancy Registry finds no apparent increase in the frequency of specific defects with first trimester exposures and no pattern to suggest a common cause. However, potential limitations of registries should be recognized.

The APR is funded by pharmaceutical companies listed here. And the APR always wants to acknowledge the outstanding efforts of the clinicians who submit cases as well as the valuable contributions of our Steering Committee. And we'll get into the governance structure of the Steering Committee a little later on.

I'm going to talk about some of the advantages and challenges of the complex multi-drug registries. So, despite their complexity, multi-product or disease-based registries have

distinct advantages over single product registries. They are logical in that they avoid duplicate efforts in the establishment of the registry, but also from a reporting perspective for health care providers, pharmaceutical companies, and regulators. They are economical, pooling resources and budgets from multiple stakeholders. Not only are multi-product registries more efficient with their use of limited budgets and resource but with their utilization of experts in the roles of Advisory Board members and birth defect evaluators.

I will touch more on analytical considerations later, but multi-product registries are methodologically advantageous to the standardization of data collection, case evaluation, and statistical analysis, not to mention enhanced validity and power.

Multi-product registries reduce competition for eligible patients and streamline health care provider participation. They also offer a more robust consolidated awareness effort.

The most important advantages, however, are from the clinical point of view. Multi-product registries serve as a centralized resource for patients and physicians. They minimize the reporting burden of health care providers, increase incentive to participate for providing a single comprehensive reporting mechanism. They offer a coherent assessment of the available data. And they provide a consistent message of the current understanding regarding risk.

Despite the many advantages, there are several challenges. I call these the C's of multi-product registries. First is complexity. They are operationally and analytically complex and require a high degree of expertise to implement.

Collaboration. They require agreement from companies competing in the same therapeutic area to work together, adopt common processes, adhere to policies and timelines.

Communication. All parties must respect the established lines of communication, which

should be appropriately documented.

Competition. Innovator companies, being the first at the table, are frequently responsible for the setup and implementation of such a registry.

Confidentiality. It is necessary to have sensitivity to the proprietary aspects of drug discovery, marketing, and lifecycle management as well as direct communications between regulatory agencies and pharmaceutical companies that may occur outside of the context of the registry but which may have relevance to the registry itself.

And commitment. Various stakeholders may not have the same level of commitment regarding their participation.

Analyses of multi-product registries can be multi-tiered. They can be at the individual drug class level, they can compare monotherapy versus polytherapy, or they can look at the overall registry experience for all the drugs being monitored. We have had an in-depth review

already of comparison groups and potential confounders. So we'll move past those topics.

In regard to special considerations, as a mentor of mine likes to say, failing to plan is planning to fail. And that is certainly the case when it comes to registries. They require unique approaches in the design, data collection, statistical analysis, reporting, and the dissemination of data.

An imperative to the success of any complex collaborative registry is to have a well-defined governance structure. By "collaborative registry," I am referring to one in which multiple stakeholders work together to meet one or more specific objectives, whether this is by choice or by mandate.

This figure depicts the governance structure of the Antiretroviral Pregnancy Registry, which is overseen by a steering committee comprised of three groups. The Scientific Advisory Board is made up of experts in the appropriate fields from academia, government,

and private practice. The advisors provide scientific oversight as well as review and interpret the data. The sponsor representatives from the pharmaceutical industry oversee the registry management, budget approvals, and regulatory reporting. The Registry Coordinating Center is responsible for the managing daily operations from enrollment to data collection, statistically analysis, report writing, interactions with the IRB, and facilitating the interaction of both the advisors and the sponsors. The primary benefit of such a governance structure is the clear separation of scientific, financial, and operational activities.

When planning research, it is vital to consider both the business and the scientific objectives and to find a balance. Business objectives address marketing, treatment options, satisfying post-approval regulatory commitments, or product differentiation while scientific objectives address product effectiveness and safety, cost versus benefits, patient/physician

satisfaction, utilization patterns, and patient adherence. Without sensitivity to the business objectives, which often drive funding sources, the scientific objectives may not be realized.

In order to alleviate some of the uncertainty with regard to preferred methodologies and design strategies, it would be helpful to have the following updated regulatory guidance that specifically addresses best practices, gives directives, unacceptable recruitment methods, and encourages consistency across therapeutic areas.

In conclusion, the implementation of an effective pregnancy registry hinges on identifying the most appropriate design. Expert consultation is a critical step in understanding the regulatory landscape and drug or population-specific nuances. Engaging stakeholders to gain broad participation and planning early to ensure the greatest utility is realized.

Thank you.

(Applause.)

DR. TASSINARI: Clarifying questions

from the panel?

DR. IYASU: Well, thank you very much. That was a very nice presentation. It's great how you discussed sort of the governance structure, which is a very important element in terms of success of such registries. Could you speak to the issues of the trade-offs between product-specific analysis versus sort of the aggregate because, you know, there are multiple pharmaceutical companies involved here? So how is that achieved, actually, in terms of data sharing about information about product-specific issues?

DR. ALBANO: The way the APR conducts its analysis, INC Research serving as the coordinating center for the registry, it is responsible for collecting all the data. They hold the data. And they analyze the data and distribute it in aggregate to the participating manufacturers and the advisory committee who reviews the data semiannually. So we have a threshold that has to be met before we do product-specific analyses. And those are all done as per

the routine analysis that is already planned out for the registry and reported as such. So everyone has accessibility to all the products. We do, you know, hold that threshold until we get a sufficient number of exposures before we conduct that.

DR. TASSINARI: I'd like to introduce Dr. Adel Abou-Ali, who is our industry representative. And he is going to speak on data collection and experiences with vaccines.

DR. ABOU-ALI: Thank you very much.

DATA COLLECTION/EXPERIENCE WITH VACCINES

DR. ABOU-ALI: As a start, I would like to thank the FDA for inviting a representative from the vaccine industry for such an important event. This is my first presentation on this particular topic after moving from government to the industry. And I will present another similar topic at the WHO in Geneva next month. And I have to admit putting those slides together was really challenging, even though in the drug arena, there

is a lot and plenty of information available on drug exposure pregnancy registries, but for the vaccine industry, the picture is slightly different. So it was kind of challenging to put those slides together on the data collection and experience with the vaccine.

Quick background. As Dr. Iyasu and Dr. Sahin, Dr. Diaz referred in their backgrounds, the importance for pregnancy registry in the vaccine industry is very similar to drug registry/pregnancy registry. The preclinical data and the premarketing safety evaluation do not provide enough information about the safety for vaccines, very similar to what is happening in the drug arena.

In addition to that, there is a theoretical risk of fetal transmission in some kind of particular vaccines, specifically for those vaccines like MMR and varicella, that might cause a risk by transmission to the fetus. Also, recent recommendations recommend giving the influenza vaccines and Tdap vaccines to all

pregnant women. So having information about dose exposures is of particular importance.

In order to give a quick picture about how it is within the vaccine industry, I found a report that was prepared in a similar meeting at the EMA, European Medical Agency, about the overview of pregnancy exposure registries, very helpful to describe how it is in the vaccine industry. They referred to the sources of pregnancy registries according to who said pregnancy into certain classifications. This classification includes that pharmaceutical companies may be responsible for pregnancy exposure registries. It could come from academic groups. It could come from research groups. And there are other new and alternative sources, such as the health care databases, like the CPRD, and the population-based surveillance registers, such as in Northern countries or Scandinavian countries.

Pregnancy exposure registries can also be classified according to the exposure. It could

be a single drug registry or a drug class registry or a disease registry. In the vaccine industry, the most common one is the single drug registry. In my limited exposure so far in the vaccine industry, I didn't see any multiple drug registries or drug class registries. It's all with a single drug registry.

It also can be classified according to the location and to country-specific and international. So far the most common is the country-specific registries. But I can see that we're moving slowly toward the global registries. We just started the new global registry for the flu vaccine QIV. It is going to be here in the United States as well as in Europe. And I think other companies are taking the same approach slowly.

In establishing the registries, the vaccine company depends basically on guidance from regulatory agencies. Here in the United States, one of the guidance for industry is one of the important guidances that we are using to establish

our vaccine registries, in addition to the reviewer guidance that came in 2005. Both of them provide very useful information about how to establish the registry. And I'm going to use the elements that were explained in the guidance that was published in 2002 from the FDA to try to walk you through how we establish our pregnancy registries in the vaccine arena.

The European Medical Agency came out with similar guidance in 2005 and described the process in a very similar way. So these guidelines provided six very important elements that we use on a regular basis when we are trying to establish our registries, starting from the design to equipment, the reporting sources, explaining how to collect the data, and how to make the follow-up, how to conduct data analysis, and how to report the results.

Starting with the design, as Dr. Holmes referred in the beginning, pregnancy registries are observational and not interventional. It's noninterventional. It's either active

surveillance or passive surveillance according to the description in the FDA guidelines. In the drug arena, the most common form is the active surveillance or the cohort even monitoring registries. In vaccines so far, what I have seen in the industry of vaccines, it is mostly passive surveillance observational studies. It could be prospective or retrospective. And, ideally, it should be prospective to avoid some kinds of biases. Prospectively means that you start enrollment prior to pregnancy or early during that pregnancy. And we're going to explain this in details.

So in general vaccine registry, we use passive surveillance. And this passive surveillance is basically the women on voluntary participation. It's dependent on spontaneous reporting.

It's a HIPAA-compliant system for most companies, including Sanofi Pasteur. And it mainly aims to collect data and information on the vaccine exposure and the pregnancy outcome in

order to monitor for any potential safety signals. So it's a mean for signal detection in other ways or in other words.

The enrollment in those registries is usually, as explained earlier, prospectively or retrospectively. So when we receive the cases or when the registry is being defined after the exposure of the vaccine but before the conduct of any prenatal tests or knowing what is the outcome of the pregnancy, we consider this prospective. Retrospectively, on the other hand, is when the registry is notified after the outcome of the pregnancy is already known. And usually this happened from the patient, not from the health care provider.

The second element in the guidelines that we use in our vaccine registries is the recruitment. The guidelines described how companies can do recruitment and announcement. And I find in vaccine, in particular, the most important way of announcement or recruitment is through labeling. Usually the package inserts

contain the phone number or a web address for patients and health care providers to how to report any cases.

The second most common way of announcement or recruitment for patients is the company websites. So far, most of the pharmaceutical companies have websites for their pregnancy registries. Sanofi Pasteur has sanofipasteurpregnancyregistry.com. GSK has a very similar one. Merck has a similar one. All of them have those websites. On the website, usually there is a description of the different pregnancy registries that is taking place, including both drug and vaccines and the mean of communications to report cases for those registries.

Other means include professional journals; professional and maternal/infant advocacy group newsletters; informational booths at professional meetings; and, finally, lectures and talks, such as this public meeting. So I'm going to show you later on our website and our

phone number, a toll-free phone number, where you can report cases. So patient or health care providers can use those means to report cases for the pregnancy registry.

The third element is the reporting sources. Usually the most common reporting source is the health care provider. Followed by the health care provider is the pregnant women themselves, who are exposed to the vaccines.

The reports can be made either by a toll-free number, as explained earlier, or from a website. Each company has one toll-free number that is for all of their vaccine pregnancies. And thorough this phone number, you can report any cases.

In addition to those reports that come from health care providers and consumers, there are other ways that we can collect data on exposure to vaccine during pregnancy. Such sources or means include company-sponsored studies. So, as you see, this is a description of the best surveillance practices we conduct at our

company. On the other hand, there are other studies that can be taking place besides this specific surveillance. Any cases on those studies can result in reports that go into the registry.

In addition to those company-sponsored studies, there is the medical literature and cases being reported to health authorities, such as the FDA.

The fourth element is the data collection and the follow-up. Usually the pregnancy cases, with or without adverse events, are being recorded in the company. Any cases that are reported to the company are being kept in a global pharmacovigilance database and are reviewed frequently by product safety officers, which in general are clinicians that reviewed those cases.

The pregnancy outcomes are followed up via questionnaire. This questionnaire is sent to a reporter, whether it is a health care provider or a patient, and collects information about different data. And this usually happens several times during the pregnancy and up to three times

following the outcome itself. So if there was a child as an outcome, we follow up for up to three times if we didn't receive any information that said, "We closed the case." Information collected in this questionnaire or in this pregnancy form would include information about the demographic data, include information about the vaccine itself, the product, the brand, and administration date. It also can include details about the pregnancy, like the gestational age, date of last menstrual period, and other information.

When it comes to reporting the pregnancy outcomes, it depends on the type of the outcome. So if the outcome for certain criteria to be considered, severe adverse event, which may include the spontaneous abortion, stillbirth, congenital anomalies, according to the Title 21 of the Code of Federal Regulations, we have to report those within 15 days besides having them in our global database.

If the outcome does not fulfill this, usually the event being kept in our global

database and reported to a regulatory agency through the periodic safety update reporting systems, which is different from one agency to another. And those kinds of evidence include all other cases of pregnancy, that do not meet any definition of seriousness and that also include all of the serious adverse events that were reported earlier within 15 days.

The last element of the guidelines that we usually follow when we establish our pregnancy registries is the data analysis. We usually analyze the data being collected prospectively and retrospectively separated from each other. For the prospectively collected data, we usually certify them according to the pregnancy outcomes. So we would classify by spontaneous abortion, elective termination, fetal death or stillbirth. We classify by live birth, also congenital anomalies.

If the information or the data is collected retrospectively, we only consider it for qualitative evaluation. We do not consider it for

quantitative evaluation. Each of those cases reported either prospectively or retrospectively is evaluated for the time of exposure, the time of conception, the maternal age, the medical history, also for biological plausibility, and any drugs that have been taken besides the vaccine during the pregnancy phase.

From the analysis, we can get occurrence rates and calculate them. And from those occurrence rates, we actually can find out if there is some potential signal or not. And if there is a potential signal, we can act accordingly.

The challenges and limitations we face in the vaccine industry so far are not so different from what drug exposure pregnancy registry is facing. We face the same limitation of completeness of data. Usually we do not have enough information from the data collected, especially if the reporter is a patient, not a health care provider. There is a lot of missing data on the branding. And to be more specific,

there is also missing medical confirmation, specifically if it was provided from the patient, not from the health care provider. We also face challenges with loss to follow-up. If the health care provider has contact with the women after the outcome takes place, then he would have a follow-up, but if not, then there is no way to have a follow-up on such cases. We also face a challenge with lack of precise denominators since this is basically a passive surveillance system, which is basically dependent on spontaneous reporting. We do not have usually a precise denominator, which affects the calculation later on. We also face challenges with the control and unexposed group.

Walking through an example from Sanofi

Pasteur pregnancy registries to highlight what I have explained earlier, Sanofi Pasteur so far has four active pregnancy registries: one for Menactra, Adacel, Fluzone, and Fluzone QIV. And Fluzone QIV, it's a global pregnancy registry that we just started. So it's

kind of an educational experience for us to explore how to do this thing globally, which will include a totally different set of challenges and limitations.

An example of the Adacel, for example, to explain the limitations we are facing, in a period of six years, from June 2005 until June 2011, we received 577 pregnancy reports. Ninety-two percent of those reports were spontaneous reports, which is the 528. And 49 study reports, which is about 8 percent of the reports, came from other studies. Out of the 528, we had 345 lost to follow-up, which is about 67 percent of the pregnancy. So this can give you an idea about how limited this process is and the challenge we're facing in this. This is not in particular to Sanofi Pasteur vaccine registries, but it can apply to other registries as well for other companies.

In summary, in the vaccine area, the pregnancy registry is a mean for signal detection. It does not answer the question, but it can help

you identify those potential signals that need more investigations and more studies. In other ways, vaccine registry can act as hypothesis-generating studies by detecting adverse pregnancy outcomes that may warrant further investigation. Having said that, despite the current limitation of vaccine pregnancy registries, it remains an important source for information.

Thank you.

(Applause.)

DR. TASSINARI: Questions? Comments? Yes, Mike?

CLARIFYING QUESTIONS FOR THE PRESENTERS

FROM THE PANEL

DR. GREENE: For the post-marketing surveillance studies that are not required as part of the approval of the drug, what expectation or requirement is there for the registries to report their data to the FDA or does the FDA find out about it by reading about it in the newspaper?

DR. NGUYEN: For the ones that are not

PMCs and PMRs if this is what you're asking, occasionally we get courtesy copies of information. And in other ways, we do detect it through our routine surveillance of the literature.

Additionally, we also have the advantage of our partnering very closely with CDC in the Immunization Safety Office. And together we often monitor the literature that way.

DR. YAO: I can also speak to the points that were brought up that there are other separate reporting systems for the requirements to report adverse events, et cetera, et cetera. And sometimes in that context, we will find out this is how they were obtained. But it's not, as you point out, a requirement if we didn't ask them or tell them to do it.

I think in most cases, companies when they are interested in trying to do something like this will actually, you know, come to FDA and talk to that, "What would be the way to best do it? How would you like to report it?" Then there is some

collaboration there often.

DR. TASSINARI: I wondered if you could expand a little bit about the challenges you are facing maybe in alanning for moving to the global registry, as you alluded to.

DR. ABOU-ALI: Well, as I mentioned, this is new experience for us. And we're moving slowly into it, but we are considering some nontraditional ways of doing that. The first is going to be in Mexico, for example. And we're thinking of using a web-based system to collect the information and establish a pregnancy registry.

So, instead of using a paper-based method sending that questionnaire to the health care provider or to the patient and then collect the data back, the health care provider, all the patient can report through an online web-based system application, that that's found online. Other ways is to use Smartphone applications, for example. And we're thinking seriously about doing this with the QIV, Fluzone QIV. Most of the

people right now have Smartphones. And everybody is using it for regular activities. So if you have an application that you can report the adverse events through, this can facilitate the process and increase the enrollment rate as well.

So those are some kinds of alternative methods that we're going to be using. Of course, there is a lot challenging or challenges to do that, but we are trying to overcome those.

DR. TASSINARI: So, I mean, those sound like approaches that one could take, whether you chose to be within the United States or global or not. I think they're great thoughts in terms of meeting some of the challenges we have.

I guess I am still trying to understand what it is that makes it so much more challenging. If you could elaborate a little bit more on why? Why wouldn't you move to a global setting?

DR. ABOU-ALI: Why would we move to a global setting, rather than --

DR. TASSINARI: Well, I got why would you move to a global setting, but what are you

anticipating that makes it more challenging than just setting up a registry within the United States?

DR. ABOU-ALI: Well, definitely you will have a larger sample size probably if we're moving globally, not just locally. This is one of the things. You are increasing your sample size. So we hope that doing a global registry will do that.

Other things, lately we have been facing challenges with other regulatory agencies when they approve the product. If the trial is being conducted in the United States, for example, and not in South America, they think that the drug might have different effects, especially with regard to the safety. So if you apply the same concept on pregnancy registry, the same thing. So they would require something locally there.

So from a resources point of view, it is easier for us to have this pregnancy registry globally, rather than having multiple local ones. So that's another thing that we're thinking of.

DR. DANA: Again, Adrian Dana from

Merck. Maybe I can answer some of the challenges that we have faced with at least maybe not global but multinational registries.

One of the things that is very difficult is the differing privacy regulations. So, for instance, we have had registries in Canada. Canada is very difficult because we are not allowed to go back to the patient or the provider to get the follow-up data, which is absolutely critical. We have to go back at the time that we, you know, expect delivery to have occurred to find out the data. So that has been extremely limiting for us.

So I think one of the major challenges is differing privacy regulations among different areas. Another challenge, of course, is that, you know, up to now, you know, finding this control group is like the holy grail, you know. And so up to now, we have largely been using, you know, basically epidemiologic data from that population. So when you start to get into other regions of the world, you know, the background rates of various adverse events in pregnancy may be differing. And

so we have to find a proper comparison group. And I think those are two of our major challenges.

DR. TASSINARI: I actually think that -- okay. Michael? Sorry.

DR. GREENE: Just as a practical matter, in a scientific advisory committee that I sit on, some of the international reports that come in report complications of pregnancy and/or birth defects in their native language, for which there is no direct translation into English. So that sometimes I will look at a report and it will be translated into English, but it doesn't mean anything in terms of any of the categories of disease that we understand. So it's harder.

DR. NGUYEN: I just wanted to follow up the question on your implementation of web-based protocols and Smartphone applications. Have you found in the early experience or in maybe pilot programs that it has helped address the 67 percent loss to follow-up or is it only to improve enrollment?

DR. ABOU-ALI: Well, it's only going to

be only to improve it. So probably we're going to have some loss. I'm not sure how big it is going to be. But there is only one published study that came from, if I recall, Malaysia. That is where they had a pilot study on a vaccine surveillance through mobile devices. The loss rate was about 70 percent as well. So it's about the 67 percent of what we're facing here. But considering that this is going to be an easier way for patient and physician and current time to report, I think it deserved to be explored.

TOPIC 1 PANEL DISCUSSION AND Q&A

DR. TASSINARI: Well, then I think what we shall do is move into our discussion session. We have three questions. They really are focused, as was this first topic this morning, around the pregnancy exposure registry. If we could have the first question? What we would like to do is canvass your thoughts and, you know, of all kinds and have a discussion a little bit about these exposure registries and specifically what the advantages have been from our experiences and what

the challenges are. And I think we have begun to hear a few of those, in fact.

The second question, just to anticipate things, is, how can we fix some of those challenges? But if we can focus a few minutes on what they are and what our experiences have been on the pregnancy exposure registry itself will then flow into, I hope, some thoughtful suggestions for solutions.

So I will open this up. I don't know if anybody would like to do this.

And, Vicki, you have something?

MS. MOYER: Just a reminder if you could please state your name before you speak for the benefit of the transcriptionist as well as the folks who are joining via webcast who can't see us all. Thank you.

DR. CHAMBERS: This is Tina Chambers. I had a question related to the prospective nature of pregnancy registries. And maybe this is something that Michael Greene or Lew can answer. I wonder whether you have seen over time or going

forward that the sort of definition of prospective is a moving target as prenatal diagnosis moves earlier and earlier in pregnancy and even pre-implantation diagnosis is taking place. And do you see this having an impact on, you know, what actually qualifies as prospective?

DR. HOLMES: Let me just tell you what we are seeing in the North American AED Pregnancy Registry. If you go across the United States, there are enormous -- and Mike knows more about this than I do -- variations in obstetrical care. And it's the old East Coast-West Coast. You tend to have the newer technologies more likely to be occurring there or, say, in the center of the country, in the Chicago-Ann Arbor area. And they have larger areas of the country that are using the old systems. And there's a slower process in moving to cell-free fetal DNA and that sort of thing.

But Sonia's analysis emphasizes the fact that we have to really be careful in our interviewing to be sure when a woman is enrolled

as a pure prospective enrollee, that that really is the case.

So you are absolutely right. It is changing. And there are occasionally birth defects now picked up at 10, 11, 12 weeks. So since we started in 1997, there has been a dramatic change. Yes.

DR. GREENE: So Lew's example of prospectively ascertained hydronephrosis is a good example because it is easy, relatively easy, by ultrasound to determine tissue-fluid interfaces and something like hydronephrosis jumps right off the screen at the sonographer. But that's not until relatively late in pregnancy. So if a woman had an ultrasound examination at nine weeks when you can't see fetal kidneys and it was normal but later you discover that there is hydronephrosis during pregnancy and then maybe even later, during the pediatric period, it's dismissed as not really being an issue, was that truly a prospective case because she had an ultrasound at nine weeks with respect to hydronephrosis?

You are right. It is a moving target, not only in technology as technology evolves but also as the embryo changes and fetus changes in terms of the diagnosability of birth defects.

DR. HOLMES: Melissa, I have another question to put on the table which is an issue for us and I would suspect it is for most pregnancy registries. And it relates to this issue that was referred to with regard to the privacy issues in Canada. About a third of our enrollees are unwilling to sign the forms to obtain copies of the pediatric records on their infants. And I don't get to talk to very many of them, but when someone does get to talk to her about why she doesn't want to do it, unfortunately, the reasons are rather diffuse. And they're usually based on fear that somehow this information is somehow going to be to the detriment of their child. And we can't really very effectively debate that with her.

So that's a reality of a pregnancy registry. And so when we publish our results, we

divide the results between those where we have the pediatric records to confirm what she has reported and those where we don't. And usually they are similar so that we are not concerned that we're missing a lot of major problems. But if you're working from the statistical standpoint, you are cutting your sample size by a third because, you know, you are already down to the pure prospective enrollees. You're down to the ones that let you get records. And it just keeps cutting your sample size more and more.

And I think this concern and worry and whatnot will continue. I think it's just going to remain a reality for pregnancy registries. So I think in advising companies on setting them up, it will be important to emphasize the need for making sure you know the status of a woman's pregnancy at the time she enrolls as well as meaningful discussion of this issue of trying to get her to give written release with her signature on it.

And our suspicion is some of it is women are just worried that somehow the data will be

used against their baby, but I suspect another part of it is, you know, she signed up because she was worried. If you contact her after the baby is born and she sees the baby is fine, that changes her motivation.

And so one of the issues that we struggle with is trying to get her to sign the forms before the baby is born. And then you've got the clock ticking in terms of how long is that signature valid. So it's a very delicate dance.

We started for the last two or three years to encourage the research assistants when they talk to her at enrollment to tell her "We are going to ask you to sign for the release of these materials." And if a woman says at that time, "I really don't want to do that," then we don't enroll her.

So we've got a third have said, "Yes, I'll give you permission to do that." And then when the chips are down, they won't do it. So it's a recurring constant, I think.

DR. TASSINARI: I think, Dr. Conlin, you

had a comment?

DR. CONLIN: I did. And it might not flow completely well with what is being discussed now. But we have a unique population, I would say, at the military. And with our active vaccine registries, I think over time, we have really seen a change in enrollment.

I think when we started with smallpox more than ten years ago, there was a concern about that vaccine. So people were eager to enroll and eager to participate. The preventive medicine side is happy that we decreased the number of women that are inadvertently exposed. But then that does decrease your potential pool of enrollees to the registry.

And then I think more recently now with the advent of Smartphones and less landlines trying to contact women, it is very easy for them, as someone just mentioned, to enroll because they are worried. But then when you try to follow up with them, they know your number. They're busy. They're not as concerned anymore. And it's

increasingly easy for them to ignore your calls.

And, for whatever reason, they don't want to unenroll or say, "Please don't contact me again," but a lot of time and resources are spent trying to contact women that are no longer motivated to participate.

DR. TASSINARI: Thank you. I would actually like to swing back to the question that started us off here with Tina because if, in fact, the definition of the term "prospective" is a moving target and we're using that definition as a central piece of how we define a pregnancy exposure registry, what is that doing for our registries? And is this something that we need to more precisely define, define differently? How could we, you know, move forward if this is the case? Where is the line?

DR. DANA: This is Adrian Dana. I think there is one place where we should perhaps make a distinction. And that is between drugs that are specifically indicated for use in pregnancy, like influenza vaccine and other drugs that either just

because the mother has a condition that needs to be treated or there's just a complete inadvertent exposure, you know, they didn't know they were pregnant and they got exposed.

So I think that we have an opportunity for drugs that are actually indicated in pregnancy to truly enroll these women before they are on the drug or before they are exposed. So I do think that distinction is important because, although we may not have maximized that opportunity, we do have an opportunity for a true prospective enrollment in those particular cases where we can enroll before exposure at least. Otherwise, it is sort of a slippery slope. And we currently are just saying, "Well, before we know, you know, that a prospectively enrolled patient is one who is enrolled before we know the outcome."

DR. GREENE: Mike Greene. As a practicing obstetrician, there are real issues with prospective enrollment for medications that you are supposed to be using during pregnancy.

The immediate question that comes up in

the patient's mind is "What do you mean you need to find out whether this stuff is safe? I thought you said you were giving it to me because it is good for me and it is going to protect me from" you name it: influenza, pertussis, my baby from pertussis. So there is a mixed message there. And we have to be very careful how that is perceived by our patients.

DR. TASSINARI: Yes, Tina?

DR. CHAMBERS: Tina Chambers, changing topics, but I agree with that totally. That's a big communication issue of how you get that across to the patient that it's for the greater good. A question about challenge in design of pregnancy registries is how to know what is an appropriate sample size. So Mike brought up the issue previously of, you know, maybe the success of a pregnancy registry for a high-risk drug is that you don't enroll anybody.

But the thing that we struggle with in our work is trying to be clairvoyant about what the number of exposed pregnancies is going to be.

And I think that is a challenge and maybe something that could be addressed in terms of identifying better ways of kind of monitoring the landscape for the number of exposed pregnancies that are taking place to determine if a pregnancy registry is meeting the mark or not meeting the mark and if the sample size that is developed for a pregnancy registry is realistic.

COL COSTER: Trinka Coster here. Yes. I think that the kind of work that we do and I know that the VA does and the sentinel folks have done I think could probably assist with the registries in knowing what the exposure, whether it's accidental or intentional, is of a pregnant female to a particular drug, especially if it's a new signal put out or a new alert by FDA put out, you can then have a nice marker of data saying what was the exposure rate before the FDA alert went out and what is the exposure rate after the FDA alert out, just on drug utilization, to kind of know if you're doing a good job or not.

And then also what Dr. Greene had

mentioned is, you know, did we register everybody that we could. I think, again, you can look at the exposure of your pregnant females in large databases and just ask, you know, are we seeing what we would expect, you know, one percent exposure rate and are we really seeing that and that would translate to no. Then we wouldn't expect anybody to register based on prior studies that, you know, you wouldn't find that.

So I think there's a use for still having the registries be the gold standard. You know, is this a problem due to this drug but using the observational and large databases to kind of assist with what is the exposure out there as well as even messy, unvalidated outcomes, maybe perhaps, to give a ballpark figure of should I publish this or should I not and what are you seeing in your observational databases?

DR. GREENE: Mike Greene. I'll refer to one of Allen Mitchell's publications since he isn't speaking up. Where he showed very nicely that when you asked women about medication

exposures, you get an increasing response rate the more specific you get about what medication you're talking about. So if you ask women, you know, "Did you take any medications during pregnancy?" you get a certain response. Then you say, "Did you take anything for colds? Did you take anything for your fever? Did you take anything for headache?"

You get more response. "Oh, yeah. I took" so and so.

And then when you get very specific, "Did you take any aspirin? Did you take any Tylenol? Did you take multiple vitamins?"

Then "Oh, yeah. I took that stuff, but I didn't think of that." So that speaks to how do you know what to expect because there is not a uniform way of collecting the information.

And one other point that I'll make is that I increasingly see a lot of women who are taking medications that aren't in the formulary. Okay? And I don't have a clue what's in those things. And they have names that are very warm

and fuzzy, but the content is very fuzzy.

DR. MITCHELL: It's Allen Mitchell. He provoked me. Yes. I just want to reinforce Michael's point -- you know, excuse my voice -- that when we talk about medications, whether we're talking about an exposure of interest or a potential confounder or risk modifier, we really need to know information about the full complement of exposures, which includes OTCs, herbals, supplements. And God knows what's in those. We also need to know about periconceptional folate. I mean, if we are looking at birth defects, it is hard to imagine a study that doesn't have information on periconceptional folate, particularly where you have upper SES women preferentially enrolling where the rates of exposure may be higher, because that clearly is a risk modifier, if not a confounder.

So, you know, I think how you asked the question is certainly an issue. I think just while I'm thinking about it, in terms of the size of a registry, there are the issues that Tina and

others have raised about trying to predict what is a useful size, but I also think that it's unrealistic to imagine that one could have a registry in sufficient time to be useful, I mean, less than 30 years, where you would have enough exposures to be able to identify risks and safety for very rare defects. And, in fact, I would argue that for very rare defects, there may be no studies that can provide usable information.

The flip side of that is for very rare defects, the public health implications are minimal. We worry about defects that occur in 1 in 1,000 women. If the risk of a defect that normally occurs in 1 in 10,000 is tripled, we are still talking about 3 per 10,000. It is certainly devastating for the affected patient, but in terms of a public health issue and a regulatory issue, it seems to me that it has less importance.

So I think that as we think about pregnancy registry, -- and I'll talk to this point tomorrow -- the most useful aspect is for reassuring that we're not dealing with a

Thalidomide or an Accutane. And then the size issues become problematic given costs and time as we try to hone down on more specific malformations and particularly rarer malformations.

DR. YAO: I would like to ask the panel off of what Dr. Mitchell has just said your thoughts, your opinions about, okay, so we're not going to be able to do something for 30 years. And we're not going to pick up necessarily the ultra rare. So what can we do? How can we modify the current state to maybe decrease the time, maybe decrease the patients?

I think that Dr. Holmes' presentation is very compelling regarding the use of a concurrent control group. I think that if we're talking about the efficacy side, we ask for control studies to try and cut down on the number of patients that you need to establish efficacy. Can we do that in a way on the safety side post-marketing that would help us decrease the time or number of patients overall to assess a signal? So I would like to hear the panelists' comments about

that.

DR. HOLMES: Let me give you my comments. It's Lewis Holmes from the North American AED Pregnancy Registry.

When you are beginning your pregnancy registry, your challenge is effective marketing. And the cost of marketing varies quite a bit depending on how aggressive you are. And that was one of our real dilemmas. We were fortunate in that in our surveys in Boston, we knew that about 1 in every 250 women at delivery was taking one of these drugs. So it's a relatively common exposure.

But, even so, mailing lists of the Society for Maternal/Fetal Medicine is an expense. Sending a letter, instead, to all the members of ACOG is a huge expense; same for the neurology groups, the epileptologists versus all neurologists; sending advertisements to primary care physicians, who prescribe Topiramate for migraine, not for epilepsy. I mean, you just face endless theoretical possibilities at how to reach

people.

And there's a huge delay before you begin to get enrollment. And you don't really know why anything has worked. Ultimately, it became apparent that there is a group of people that we call cheerleaders, who are the folks who are really aware of the registry and really actively encourage their patients to sign up. And, obviously, you would have loved to have found the cheerleaders in the beginning. And you could send all of your mailings to those people and not the thousands of folks who are going to throw it away.

So if you're trying to make a registry more efficient and get answers sooner, it's the front ending, more money for marketing to me would be -- if I had to do it all over again, I would want to have more money so we could really start spreading the word faster, beginning the process, ultimately finding those people who are helpful. And that would be my advice to anybody. Don't do it on the shoestring because the chances are it will drag out and wear out everybody's patience

and tolerance and never get anywhere.

DR. TASSINARI: It sounds like we may need to phase out the word "passive" in our description of what these programs are designed to do because I think, as you say, it really all depends on how well you get off to a start.

Tina?

DR. CHAMBERS: Adding to what Lew said in responding to your question, I think that it depends on the drug and the disease, too, and how commonly it is going to be used. So maybe the realistic, you know, perspective on a drug that is going to take 30 years to accumulate enough exposures to say something is to set the goals of the registry to something that you can do in an interim or more reasonable period of time.

And I think it is important not to lose sight of the fact that pregnancy registries aren't just about major birth defects. They're about looking at a spectrum of outcomes that we know that known human teratogens are typically associated with. And I think that is one of the

great advantages of pregnancy registries, giving an early sort of snapshot view of is there an increased risk for reduced birth weight, is there an increased risk to the extent that you can look at it, spontaneous abortion or preterm delivery? And if you are looking at that broader range of outcomes, it becomes increasingly important to be able to have an internal comparison group.

DR. HERNANDEZ-DIAZ: I think that's a good point. I'm so far being realistic with the goal. So if because of the use you can only possibly enroll 50 women, then that's what you can do. And then the question is, what would be the goals of that registry and how to report with a confidence around what we can report. But following up on your question about controls, such as wanting to add to the internal non-exposed control group that in the disease-based registry or multi-drug registries for similar indications, one of their advantages, I think, is that they allow us to assess comparative safety, comparative effectiveness. That is such a hot topic. So they

will allow us to compare drugs with the same or similar indication. And I think that has the advantage of having the internal control group with the same methodology, same diagnosis of the outcomes, but, you know, that's another thing.

There are two more advantages to them, that, first, you have women with the same indication so that they will have a more similar background of certain outcomes to the confounding because of indication will be lower. And also they may respond to the clinically relevant questions of which medication to use to treat these specific women when we are dealing with diseases that treatment is necessary for pregnant women. So when possible, I understand it is not possible for all registries, but having these multi-drug registries I think add these additional advantages.

And I know that they are logistically complicated for the reasons mentioned. But I think that could be another thing to consider for controls.

DR. BERLINER: I just wanted to comment on some of the things that I heard that seemed a little contradictory. So one thing I heard is that women are enrolling in these registries because they're worried, which sounds like they're misunderstanding that the registry will help them personally versus contribute to knowledge and then the other issue of that people are -- you know, that maybe physicians don't even want to mention the registry because it will make the patients worry.

And so I sort of wonder what the best practices are, you know, and having gone through pregnancy myself, you know, what the best practices are where you have a conversation with your doctor at the time that you are thinking of getting pregnant or you find out you are getting pregnant, you are pregnant, about whatever your medical conditions are and what is known about the risks and benefits of continuing your medication, what the alternatives are, what the potential

risks to the fetus are. And I think that conversation has to happen in every single case. And so part of that discussion could be or should be what is unknown about the risks and then if there is a registry inviting the person to participate, not because it will help them but because it will help other people.

And, you know, I know from other registries I worked on on, really, widely varying topics that, really, people are -- you know, that they are altruistic and that they do want to participate in that if they really understand. And so I am just wondering about other people's thoughts on that.

DR. GREENE: Mike Greene. Some of this is anticipating a little bit of what I am going to address this afternoon in my talk, including a recommendation for a way of possibly improving registration of exposures in registries, but one method that I would like to mention that Allen did very successfully with the Accutane registry was to say to women who were receiving prescriptions

for Accutane, you know, you're not supposed to get pregnant when you're taking this stuff, but with the prescription, it says, but, you know, if you accidentally do, please call 1-(800). And how did you do that, Allen?

DR. MITCHELL: Well, actually it wasn't quite that.

DR. GREENE: Okay.

DR. MITCHELL: Now you are prompting me to have to recall something. So we're in problem state.

What we did was we came up with I think what was the first direct-to-consumer solicitation, where included in the Accutane package was an enrollment form. And the idea was for women to enroll in advance of potential pregnancy. Ideally, they would, you know, enroll. And we made it look as much like a toaster rebate coupon as we could, consistent with IRB and other regulations. And we paid them $10 for the effort. And the idea was to encourage them to enroll and then be followed. And we randomized them to

different follow-ups. And then we were able to identify those who became pregnant. So we had them in the system.

I'm not sure that's applicable to a pregnancy registry. I hadn't thought of it in that context. I mean, the idea of enrolling all women who are potentially at risk for pregnancy seems overwhelming for a pregnancy registry and then, you know, thinking, well, if they are exposed to a given drug, that might work for a universal registry. If there were one registry into which all women would fall if they were exposed to drugs A through Z, it might work. I'm not sure it would work in the context of recruitment here.

DR. CRAGAN: This is Jan Cragan. I wanted to get back to part of the comments on sample size and experience of the North American AED Registry when two or three cases of cleft showed up in the first couple of hundred or so exposures to lamotrigine. There were a lot of discussions. And that was not an easy discussion

about, do we release those findings? What do they mean? You know, what is this? And now we have seen the rates go down quite a bit. And there is an I think currently real interest in, oh, well, this registry has produced a lot of information. And now it's getting big enough we can look at these individual defects and we can say more about the risks of these drugs, which is true.

But I think I also have reservations about continuing to do that too much because you will see these kinds of spurious things that come up that you don't know quite what they mean. And when that happens, then you are in the position of but we have this information that might indicate it is a risk. We can't just keep that to ourselves. You know, people have a right to know what we know. And this is all we know right now and such.

So I think it is important to keep the goals of these registries in mind in the context of -- and I know tomorrow is about alternative approaches and other kinds of data sources. But

to keep the role of the registries in the context of what other kinds of studies can be done to better address certain topics and that maybe these are good for generating questions that can be addressed through other means. And that's partly GlaxoSmithKline had a registry solely for lamotrigine. And when it closed, part of the reasoning was that there are other methods and other data collections out there that can look at this better than the registry can at the moment. So I think that is an important thing to keep in mind when looking at what is the goal of our registry and how large does it need to get.

DR. TASSINARI: I'd like to get back to that just for a minute, but, Dr. Honein, you had a comment?

DR. HONEIN: This is Peggy Honein. And I just wanted to bring up the issue of adverse outcomes for a pregnancy registry and the importance of having it where possible. I think there is a real challenge with the registries only capturing adverse outcomes on the date of birth

and really missing many of the birth outcomes and essentially all of the development. And I just would like to be a part of that conversation about how we have --

DR. TASSINARI: Peggy, you were breaking up just a little bit at the end. What was that last piece?

DR. HONEIN: Sorry. The connection. Okay. I'm just wanting to think about how pregnancy registries can get all adverse pregnancy outcomes, which is certainly what the moms want to know, just for the --

DR. HOLMES: Peggy, this is Lewis Holmes from the North American AED Pregnancy Registry. We have done studies on cognitive development in children exposed to anticonvulsant drugs. And that is a real challenge. My colleagues in developmental psychology recommended that the children be at least six and a half years old at the time they are evaluated. We found that it is a very labor-intensive process. You need to get information on the mothers' and fathers' IQs and

the comparison child's parents as well as the child, incredibly expensive.

And if you are enrolling women during pregnancy for a pregnancy registry, you do have at the end, at that postpartum interview. You've got theoretically a sample size that could be recruited six years later. So in that sense, it's a valuable potential resource. But it is an issue of pick the things, the questions that ought to be asked. For example, in anticonvulsants, we would say pick the drug that is associated with a higher rate of malformations because that is the one that is probably going to have a higher rate of being associated with developmental issues. Find a bucket of money somewhere. Wait six years. And do it.

And that is not a model that is easy to move and to have in one office. You would almost want to have collaborations between us and, say, developmental psychology groups that are better set up to do the post six and a half-year-old follow-up.

Our system is very dependent on funding that is just very fragile. And it's hard to imagine how we could be fortunate enough to have resources that are ready to go as soon as these children get to six and a half. So I think it's a wonderful goal to take the additional perspective of how many of these children have problems in learning, but I'm just not sure how realistic it is given that everybody is worried about just being able to pay their rent.

DR. IYASU: So since we're talking about challenges, I wanted to go back to the issue of sample size. You know, sample size, I guess several people have pointed out that, you know, it's determined or it's based on what the question is that you're asking. And so we get protocols or proposals that would assume that sample size based on sort of detection of a twofold increase in measurement information that may be spanning multiple organ systems. And that, you know, sometimes is very difficult to interpret because thinking about how teratogens would work, you

know, you don't think of them as causing multiple issues with multiple sort of organ systems. So sort of what is the trade-off in terms of powering to measure malformations as a group versus specific, you know, defects or organ systems because that is a challenge that we have in terms of not only pregnancy registries but also in the interpretation of the data that you may get out of these registries. So what does it mean if it's, you know, 20 percent increase or 30 percent increase over background or whatever reference group you are looking at?

DR. CHAMBERS: So I think that's a really great point. And it's even further complicated by the common situation where the pregnancy registry is focused on a drug or a vaccine that isn't used continuously throughout the first trimester so you're not just talking about sample size of exposure in the first trimester. You're talking about sample size of exposure at a critical window for embryonic development, for an outcome that you're interested

in looking at. And I think it comes back in pregnancy registries where the sample size that is feasible or obtainable is smaller, that in terms of major malformations, they function as signal detection mechanisms and, as Jan says, they generate hypotheses that can be tested using other methods that really are better powered to look at specific birth defects.

DR. MITCHELL: Yes, two things. To go back, Solomon, if I can, to the previous discussion, -- and I'll return the favor of quoting Michael -- when we talk about what is a reasonable goal for a pregnancy registry, Michael uses the term "the long shadow of DES." And, to quote a previous government official, there are the known knowns and the unknown unknowns.

And I think that those of us who have been involved in this area for some years recognize that something like DES is not going to be identified in any in any reasonable system or any reasonable time. I mean, if it takes 18 years, at a minimum, to manifest the problem, by

definition, you are going to have wait 18 years from exposure.

So I think, you know, on the qualitative side of what you can identify, that's the extreme. I think the issues of development, I would echo what Lew said, but I would add more to it. And that is I don't think it can be solved just with a bucket of money because if you are going to follow up kids to age six and a half, you have to be very aware of intercurrent exposures, which can affect development. So it's not simply a matter of going back to those kids. You have to stay in touch with them and repeatedly interview the parents and so forth.

And so I think we have to be careful about what we define as reasonable goals. And I would argue that that ought to be driven as much as possible by public health concerns. So the more common outcomes, the more common disabilities are of most concern.

And then we have to look at what is feasible. I mean, are we going to be trying to

identify risks of autism for every drug that is being marketed. That is a real tough challenge. And I think we need to be able to accept the fact that there are certain things we may not be able to know or we may know them so much later than we would like.

And, just as a final point, in terms of the size of the registry, I'll echo what other people have said. And I don't think it ought to be understated. And I'll mention it again tomorrow. The value of a pregnancy registry apart from the other pregnancy outcomes that -- we're focusing on birth defects, but, as Tina points out, there are a lot of other pregnancy outcomes, adverse outcomes, of concern that a pregnancy registry can very effectively identify, I would argue.

In terms of birth defects, we really need a sort of frontline system to assure that we don't have Accutanes and Thalidomides out there. When a drug is brought to market, we really don't know in the human condition whether that drug may

be an Accutane; a Thalidomide; or even a valproic acid, which is sort of intermediate. So I don't think that we ought to dismiss their value, but I think we ought to be very careful about identifying what it is we think they can produce.

DR. TASSINARI: Well, in the course of your conversation, some of you may have noticed we switched to question 2, which asks, based on some of the challenges and advantages that we do know about registries, what are your recommendations for overcoming some of these challenges that we have been talking about in the last few minutes? So, Allen, I don't know, you know, based on those comments whether you have some thoughts about the kinds of things we should be thinking about to make sure that the pregnancy registry still is an effective or a most effective tool that we have to choose from when we are trying to get some of this data.

DR. MITCHELL: Yes. As anyone who knows me knows, I am never shy about answering a question, but on this one, I think I would defer

to many more experts in the room who have, really, hands-on experience with the registries, because I think you're now dealing with sort of the qualitative aspects of operating a registry. And that's something with which I am not as familiar as others.

DR. HOLMES: This is Lewis Holmes again from the North American AED Pregnancy Registry. I didn't say in my presentation, but I would predict for the FDA and others that if there's not sufficient attention paid in pregnancy registry design to inclusion and exclusion criteria, you are going to be presented with epidemics of muscular VSDs, epidemics of hydronephrosis detected during pregnancy by ultrasound because those designing the study didn't really go through the process of either agreeing what is a malformation and what is not. And they don't have an internal comparison group. And you're going to have that happen. And then you're going to be left with, what do we do with this now? You're basically saying you've got to start all over

again and do it right.

So my suggestion is that you guys need to put more teeth into the recommendations in terms of saying you've got to do this, you've got to do this, so that you have something well-designed or it doesn't get blessed by the FDA.

DR. CRAGAN: This is Jan Cragan. So along that line because I have had a similar feeling for a long time that, you know, there has been guidance put out, we know what the methodological issues are, there are some registries that are dealing with many of those that have comparison groups and such, and that it's sort of time to up the bar a little bit and that FDA should be able to say, rather than just "You need to do some post-marketing monitoring of pregnancies in order to market this drug, to be able to say, "And you need to do it of this quality" or "in this way" or whatever.

And I'll just share this. It has some parallels, but it's not entirely. But one of the things that has happened in the birth defects

world is the state birth defects programs -- and CDC funds some of those but not all by a long shot, and they have gotten together and, you know, many years ago wrote a guidance, guidelines for conducting birth defect surveillance that has been very helpful to new programs coming along and such. And we have, you know, some programs that are just getting started, some that have been there for a while, some that do a great job.

But what they have done over the last two or three years is to get together and try to move from guidelines to standards. And so the programs themselves, it has been with our help, our expertise. We have helped with coordination and stuff, -- but it's the programs themselves putting this together -- have started to come up with standards for the quality of the data they collect. And now they are working on the utility of the data they collect and meant as a self-assessment for the programs. It's not a grading that gets published and such but as a self-assessment to see where they are.

And so, you know, they have some standards for -- you know, if you are going to do birth defect surveillance, you at least have to do this much. And then they have standards that -- well, most of our programs probably fall within this range. And that is kind of where everybody is. And then they have sort of the gold standard of, you know, this is what everybody should be striving for.

And, as I said, they've come up with that for themselves. And I don't know if that is even possible in this range, but if there were some similar sort of set of standards about post-marketing surveillance for medications in pregnancy that FDA could refer to and say, "You need to conduct surveillance to market this drug. You need to do it at least a certain standard. And here are some programs already out there doing it," something like that might be helpful. I don't know.

DR. HERNANDEZ-DIAZ: Did you ask would we think about where measures can be best? I

think we would all agree that they are poorly best as the first line of defense against Thalidomides. So that we don't have another Thalidomide program. So with some 100 women enrolled, you can rule out huge increases of major malformations, although I think that because they can enroll specifically exposures to medications that may be, at least at the beginning, rare. They can enroll them even before large databases that need some years to have women enrolled in them, have the pregnancies, and clean the data. So I think there they can clearly be the best.

And I think, as you step away from that, that door is specifically fixed or even development problems, you not only need a larger sample size. But then the validity of every step that we discuss from perspective, personal perspective, to evaluation of the outcomes, et cetera, then you need to have better and better methods. So it gets more complicated if you try to get to more rare events or long-term events. And then you move away from the idea.

Now, where to put the line, I think it's up to discussing, but I think we all agree where the extremes are.

DR. TASSINARI: And it's the middle where we usually play.

DR. SAHIN: I have a question for Jan Cragan. The Metropolitan Atlanta Congenital Birth Defects Program is one of the most commonly used comparison groups. Could you comment? Please give us your thoughts on the appropriateness of using this as a comparator group. Thank you.

DR. CRAGAN: Sure. So I work in the Birth Defects Branch at CDC, and I am currently Medical Director of the Metropolitan Atlanta Congenital Defects Program. And that's a convenient, commonly used reference for how frequently birth defects occur generally, not just by pregnancy registries but by lots of activities, mostly because MACDP collects data on all malformations, genetic conditions, chromosomal anomalies. So it's a very broad ascertainment. And it's been in existence since the late 1960s.

So it's very longstanding with very stable prevalences, et cetera. But I have some real issues with it being used as a direct comparator for pregnancy registries.

The methods are very different. MACDP is a retrospective ascertainment. We identify children and pregnancies with birth defects by reviewing medical records at local pediatric and birth hospitals, prenatal care sites, maternal/fetal medicine departments, and such. We go to a few pediatric specialty clinics but not all of them. And it is mostly a hospital-based system. So for a child to be recognized, they have to have either had surgery or required hospital care for their condition.

It's also purely a truly population-based ascertainment. So mother has to be a resident of the central counties of Atlanta at the time of delivery to get included. And we know that the population of Atlanta is not representative of the population of the general U.S. of all pregnant women or certainly not of all

women who have a certain condition or who may take a certain drug. So I think the population characteristics may differ.

MACDP ascertains defects up to six years of age. And so, as Lew was pointing out, the prevalence can be very different depending on the timeframe. And most of the registries that I know of either collect information on the newborn or within the first year of life.

And so I think, for all of those reasons, you wouldn't expect the prevalences seen by MACDP to be similar or to be exactly the same as what is ascertained by a registry. What I have tried to tell registries is that they shouldn't make direct comparisons, saying, you know, "Is our prevalence the same as MACDP's?" If they don't have an internal comparator, then they can review the literature and look at prevalence estimates that have been published. And MACDP is one of them, but it is not the only one out there.

What I do think MACDP is helpful for is this kind of idea of applying a straight case

definition to what is a birth defect and what are the inclusion and the exclusion criteria. And there are registries that use our criteria because they're well-documented and they can call us and ask if they have questions about particular defects. And I think that application of a specific case definition is very helpful. And it's fine to use MACDP's case definition, but I don't think you would expect the prevalence seen in MACDP necessarily to be the same as what is seen in a registry.

COL COSTER: Trinka Coster here. One comment on how to maybe get more people aware of the benefit of registries is do some of the marketing that we have done with meaningful use, at least in CMS, for following metrics. We have also done it with partnership with patients. So, for example, you know, opioids. You know, everybody is talking about opioids, opioids. How many people are on it? How many people are on this dose? And essentially everybody is developing metrics for that.

I could imagine if you decided on a drug class that you were considering as concerning and you pushed that up to get a meaningful use or partnership with patients advertisement that everybody develops a metric for did you have the females, yes or no told about the registry. And at least you're getting then a metric on how many, you know, people complied with, you know, the family physicians, you know, everybody else on talking about this. And it could be a safe drug just to get females used to the fact that we have registries, we monitor this stuff, and then you kind of get a herd effect of that kind of passing over to other registries that you have.

But I know that we are all inundated at the health care places with these kinds of initiatives. But once -- I mean, they really do take hold. And it really kind of does get everybody stepping in line with doing something like that.

DR. ALBANO: This is Jessica Albano. I think one thing that would be helpful is to have

some input for industry, particularly, about what is considered appropriate versus potentially promotional in regards to awareness activities. I think that can sometimes be a big stumbling block, not doing enough or really much of anything as far as awareness to increase enrollments in a registry for fear of promoting use in pregnancy when it's not indicated for that.

DR. CHAMBERS: This is Tina Chambers. And, to follow on Jessica's comment, I think that really is important, not only understanding what you can do, but, going back to Mike's comment earlier, maybe some guidance for industry, especially for industry-based registries, about how to communicate the existence of a pregnancy registry in such a way that it isn't perceived as negative for the drug.

DR. TASSINARI: So I think we've heard several times about recruitment efforts, awareness efforts. I think that is a great term. Are there any other means to address this, what appears to be a constant issue of struggle to enroll in a

registry? I'm also struck, too, by the fact that very often we see pregnancy exposures reported in other systems when we know that there is a registry available. So it continues to raise this question. Is it just awareness or is there something else happening here that we should look at and address?

DR. MITCHELL: It's Allen Mitchell. I don't know the answer to it. I do know historically practitioners have been very wary of getting anywhere near the notion of anything I prescribe might do your baby harm. I think part of that is the litigious nation of our legal system. And, you know, part of it is I think from just a clinical standpoint, as Michael said, the clinicians' reluctance to suggest that there is a problem when there isn't. And how you overcome that is tricky.

But I do think that educating practitioners about the need to collect data not being a sign of danger, not being a sign of imminent harm, it's not an easy message to

communicate. And there are others who are much more expert at it.

But I think that so many practitioners when you talk to them about -- even today, I think it's less a problem, but it's still a problem. When you talk to them about drug use in pregnancy, they really don't want to raise that subject of any kind of potential risk.

And, you know, a classic example is the SSRIs, where you've got a woman in front of you who is incredibly anxious and depressed and now you're going to raise the risk in her mind about the drug you're taking for your anxiety. So, I mean, that's sort of the arc typical worry, but I think it's a major task.

DR. GREENE: Mike Greene. Melissa, your question is very pertinent. About a year or two ago, the National Toxicology Program endeavored upon a review of the potential pregnancy effects of all chemotherapeutic agents that are used for cancer treatment. And one of the biggest problems that they encountered was scrounging together all

of the case reports. And in that situation, although the medications are likely to be teratogenic, many of them, there's no central repository for information about them. Fortunately, cancer during pregnancy is relatively uncommon. So there aren't a huge number of exposures. But there is no central place to find information about the consequences of those exposures.

All of the reports in the literature are either single case reports or very brief case series. The quality of the reporting was very variable, at best. In many cases, we couldn't figure out what the gestational ages at exposure were, what the cumulative doses were, what concomitant medications may have been given. So these are problems that are very germane, even when you're giving out medications that you know are likely to be teratogenic, but you don't have a heck of a big choice because the patient is very sick.

DR. TASSINARI: Any thoughts on how to

address our issues of loss to follow-up or absence of data?

DR. MITCHELL: I don't see Tina or Diane saying anything, but I think one of the approaches I know OTIS uses is basically establishing a relationship with the consumer, with the patient. I think if you are working through the physician as an intermediary, you are dealing with an incredibly difficult challenge. And it gets worse as time goes on because physicians have a lot of other things on their plates to worry about than chasing down the outcome of patients. But when you have patients who are enrolled in the registry directly by the registry and they have what they perceive to be a relationship with the registry, a personal relationship, I think you can get loss to follow-up rates of, what, less than five percent. So it can be done.

DR. TASSINARI: What is a reasonable loss to follow-up rate in a typical registry? Is it in the 25 percent range? Should we expect, you know, 50 percent? What could it or should it be?

DR. HERNANDEZ-DIAZ: Yes. That is a good question. I think probably OTIS has the record of the lowest because women are calling. Right? So the women who are enrolled have shown an interest already.

In the North American Anti-Epileptic Pregnancy Registry, it's more about 15 percent but the same thing. Women call to enroll. And even when prescribers sometimes recommend them to enroll, they are the ones who call.

And also perhaps it also helps to have this several calls during pregnancy, say, at seven months and then postpartum so that they keep in contact.

And another thing that may help is if you wait until delivery to ask mom to complete forms and send you the forms, it may not be the best timing right after birth. So if you can get that done a little bit before, at the same time allowing enough time for you to have the records, maybe after two or more months later, that might help, too.

DR. DANA: This is Adrian Dana. I will say that, you know, I think there is a big difference between a manufacturer-run registry, where there is a manufacturer contacting a patient, and a registry where there is a health care provider that may, in fact, be their health care provider following up.

I will say that we have had a little bit better record and that our loss to follow-up, even from a manufacturer's perspective, is only about 30 percent. And I am not sure what the difference is, but we do require that there is a health care provider for enrollment so that we can both contact the provider and the patient, you know, if needed, to try to get that follow-up information.

So, you know, obviously what you are striving for is 100 percent, but I don't think that is realistic. And I think that the character of the registry, you know, you will get different rates of loss to follow-up. And depending upon who is running that registry, different rates of loss to follow-up are just going to be the case.

DR. TASSINARI: Well, then, in the closing minutes, I think I would like to move to question 3. And this is really around the topic of looking at the decisions that need to be made when you have a product that would benefit from a registry. And what are the criteria for determining whether we should have a single product or a multi-product or a disease-based registry? And which design is appropriate when? I'm sorry, Michael. Go.

DR. GREENE: Mike Greene. So I am on the scientific advisory committee for the ribavirin registry. And we have had to address this recently. For many years, we looked just at ribavirin, but in recent years, there are new protease inhibitors that are increasingly used either with or now instead of ribavirin to treat hepatitis C. And the question now came to our group, you know, should we now start broadening registration, not just for ribavirin exposures but also for protease inhibitors?

And it gets very complicated fast

because ribavirin is off patent. There are a number of companies that produce it and, therefore, sponsor the registry. Many of the companies now that are producing the protease inhibitors have nothing to do with ribavirin. And they are virtually at this point all still on patent. And it gets very complicated fast as to how do you expand a drug registry just as a practical matter.

DR. HOLMES: As I mentioned earlier, Lewis Holmes, the North American AED Pregnancy Registry. Advertising, initial advertising, is a really crucial expense and effort. And the advantage of having multiple products and multiple companies, part of that process is obvious. You know, you have a much better chance to get more support, and you have a much better chance to spread the word more widely because it's not just drug A, drug B, and drug C but, you know, a whole group.

We think of anticonvulsants being in the low 30s range, 33, 34. And that's been very

helpful.

DR. CHAMBERS: So, in my opinion, there are situations like the Anti-Epileptic Drugs and Pregnancy Registry and the antiretrovirals, where it's sort of a slam dunk that a disease-based registry makes a lot of sense. But the scenario that Mike described is probably going to happen more and more often where there is a drug and then there is another one and then there is another one and it happens sequentially. And so, then, how do you go back, then, and revisit the situation of should this be a disease or a cluster of disease-based registries?

And maybe the thought there is when you have, you know, a critical mass of several products that are coming to market when the post-marketing commitment or suggestion is made that a pregnancy registry be set up. Should the conversation be suggested, then, to be had with existing pregnancy registries that somehow could be remodeled to address the disease-based approach?

DR. HERNANDEZ-DIAZ: Sonia Hernandez-Diaz. I agree. As I said, I think that there are many advantages from a public health point of view to have multi-drug registries when there is a disease treated with several alternatives. And it improves the validity as well from a math point of view but also logistically when a new drug will come to the market, there will be the network in place to I think -- it will be easier and faster to have information ready for that new medication.

Having said that, I understand that logistically that represents making different companies collaborate and then with some of them going generic in a pattern, that may be very complicated. But I think from a purely public health point of view, they generally will make more sense.

DR. ALBANO: This is Jessica Albano. One of the other complications is not having a clear understanding from a generics perspective what the obligations are and whether or not they will be required to participate. So certainly for the

brand new products that are already there, but then once they go off patent, you know, is there a clear precedent for how, you know, that therapeutic area moves forward?

DR. MITCHELL: Yes. I just want to reinforce what Jessica said and actually extend it a little bit. For a manufacturer whose drug is about to go off patent, that issue becomes very real because the question is, should they be investiing in a pregnancy registry when, in fact, the majority of sales, the majority of the market within three or four years is going to be generic.

So I would throw at FDA's feet the issue of making generics responsible for their drugs in some way that is equivalent to the sponsor so long as those drugs are being used by pregnant women. I think that's really an issue.

DR. CHAMBERS: Just to add to that, I think we're the ones who have the one generic pregnancy registry. At least how it was communicated to us was that they were strongly

recommended that they needed to join the pregnancy registry as a group, which they did.

MODERATOR WRAP-UP MORNING SESSION

DR. TASSINARI: Well, thank you very much for this morning session. I think it has been very helpful in hearing your experiences and your thoughts, particularly around where we are in this current state. I will ask if there are any final thoughts here in the room. Yes, Mike?

DR. GREENE: I would just like to make one other comment, which is that when the basic principles of mammalian teratogenesis were being described in the 1950s and '60s, there was a straightforward correlation in everybody's mind between a drug and a malformation. And if you got a drug that seemed to cause a whole lot of malformations, people sort of dismissed it and said, "Well, you know, maybe that's really confounding by indication, you know. It's the fever that caused all of these different problems."

I think that life has become more

complicated as we have learned more about genetics and teratology and we now know more about homeoboxes, genes, and transcription factors that affect the expression of suites of genes that could make it more credible that a variety of congenital malformations could, in fact, result from a single exposure. Life is no longer I think as simple as it was in the 1950s and '60s, when J. G. Wilson was describing the principles of mammalian teratogenesis.

DR. TASSINARI: And our colleagues on the phone, any comments?

DR. CONLIN: This is Dr. Ava Conlin. No, nothing further for me right now. Thank you.

DR. TASSINARI: Okay.

MS. MOYER: So we are about to break for lunch. And we will have one-hour lunch break, which is on your own. If you are a panelist and you are participating in the lunch, we have that in a separate area for you. If you didn't participate, you can certainly also use the room. So we will be breaking for one hour. And we will

resume at 1:00 o'clock with the open public comment session. If you have not registered or let us know that you were here and you had previously let us know that you were interested in speaking, please see the registration desk so that you can check in and we're ready for you. Enjoy your lunch.

DR. TASSINARI: Thank you very much.

(Whereupon, at 12:01 p.m., the public meeting was concluded.)

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