Pregnancy Registry Public Meeting

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Food and Drug Administration

White Oak Campus

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Ms. Diana Johnson

Dr. Solomon Iyasu

Dr. Michael Greene

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Dr. Susan Andrade

Dr. Melissa Tassinari

Dr. Lewis Holmes

Dr. Alan Mitchell

Dr. Sonia Hernandez-Diaz

Dr. Lynne Yao

Dr. Jessica Albano

Dr. Arian Dana

Ms. Diana Johnson

Dr. Ava Marie Conlin

Dr. Janet Cragan

Dr. Margaret Honein

Dr. Craig Hansen

Dr. Michael Nguyen

P R O C E E D I N G S

MS. MOYER: And we are going to be starting the public comment session shortly. If everyone can please -- the panelists can please find your seats and the attendees if you can find a seat as well. We will be getting started shortly.

DR. SAHIN: Good afternoon everybody. We will now begin the open public comment session. Both the Food and Drug Administration and the public believe in a transparent process for information gathering and decision making. The comments provided during the public comment session may be considered for discussion by the panel during the panel discussion session.

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

The red light means you need to stop speaking and return to your seat.

Will Speaker Number One please step up to the podium and introduce yourself.

MS. HARDY: Good afternoon. I am Janet Hardy. I'm here representing ECCPH and I Chair a Pregnancy Registry Advisory Committee that is sponsored by Teva Pharmaceuticals.

It is my pleasure to speak to you this afternoon. And I would like to speak about classifying registry cases as prospective and the importance of test technology.

My travel expenses were paid for by ECCPH and I'd like to acknowledge again that I chair this advisory committee.

My collaborators are listed on this slide. And I'd like to thank them for their insight and contributions.

We've already seen some of this information passed before us so I am going to go quickly.

The FDA Guidance published in 2002 notes

that registries should expect to receive both retrospective and prospective case reports. Enrollments of prospective cases minimize the opportunity for selection bias and improve the likelihood of registry success. Essentially prospective means that women are enrolled before they have knowledge of their pregnancy outcome. Prenatal testing, although not perfect, may contribute to knowledge of a pregnancy outcome prior to delivery; an example being a congenital malformation. This knowledge may influence a woman's decision to participate in our registry. This knowledge and even the potential for this knowledge may also pose a challenge for case classification.

In the 12 years since the FDA guidelines were issued prenatal testing has undergone a transformation. New and updated tests are administered and provide results yet earlier in pregnancy. Increasingly sensitive tests are available including ultrasounds, scans, genome-wide binocular testing and non-invasive prenatal

pre-diagnosis; these facilitate earlier clinical testing.

Additionally direct to consumer home test kits are increasingly available further facilitating some degree of knowledge to women earlier in pregnancy. All of these can make classification of prospective case classification increasingly challenging.

The 2002 FDA guidance specifically for case classification as we've already heard is after exposure to a product but before any prenatal tests that could provide knowledge to the outcome is considered a prospective. If prenatal testing has occurred the case is usually considered retrospective. Parenthetically we can appreciate that these may leave room for ambiguity to operationalize these definitions in present times.

My colleagues and I look to publications from other pregnancy exposure registries for guidance. I am not going to go through this again. It has already been discussed, the anti-epileptic

pregnancy.

We recognize that others may also be challenged with operationalizing case definitions and with being consistent between cases. Through our experience we outlined the following guidelines:

1. The earliest record of complete informed consent establishes the date for case classification depending on the protocol oral consent or written consent may be used.

2. Ultrasounds conducted less than 12 weeks gestational age are not reliable indicators of a congenital malformation.

3. Ultrasounds conducted between 12 and 18 weeks may reveal a congenital malformation. Each individual case should be reviewed.

4. First trimester serum review screens are non-conclusive indicators of a congenital malformation.

5. Ultrasounds performed between 18 and 20 weeks may reveal a malformation and therefore would be considered retrospective.

6. Absent test or procedure information greater than 18 weeks and prior to birth may permit case classification as prospective; and 7. These guidelines should be reviewed periodically.

It is important to understand the timing, purpose, and conduct of each test. For some registries a prenatal test may not be exclusionary. The overarching point we want to make is if a registry's purpose is concerned with malformations and a specific prenatal test does not assess malformations, consider the possibility of serendipitous malformation discovery through testing. I am happy to discuss this later if needed.

Our suggested guidelines may be applicable to other pregnancy exposure registries conceptually they may also be useful to consider for the analysis of large data sources when multiple years of data are combined to increase study power.

The take-home points from this presentation are a priori defined guidelines

facilitate consistency in case classification. And advances in test technology can impact registries and database studies. Technological advancement may eventually help. Three time points converge; the prenatal booking visit, the prenatal tests and a woman's consent to participate. The purpose of this presentation was to stimulate discussion and draw attention to the importance of case classification as the FDA updates their guidelines.

Thank you.

DR. SAHIN: Will Speaker Number Two please step up to the podium and introduce yourself?

MS. GOLEMBESKY: Good afternoon. My name is Amanda Golembesky. I am the director of Epidemiology at USB Biosciences. Today I will be speaking on a methodological comparison of anti-epileptic drug pregnancy registries and their implications on estimated birth defect rates.

For full disclosure this project was funded by UCB Biosciences. And I am myself a full

time employee of the UCB Biosciences and as such receive stock options from UCB. My disclaimers are that these data have been previously published. But full references are available upon request.

To begin as we have heard earlier today there are multiple epilepsy pregnancy registries that are in existence: there is the European Register of Anti-epileptic Drugs in Pregnancy, the United Kingdom and Ireland Epilepsy and Pregnancy Register, North American Anti-Epileptic Drug Pregnancy Registry, and the UCB AED Pregnancy Registry. This list is not comprehensive but these are the four that we'll be focusing on today.

These registries all share similar objectives mainly to monitor for an increased risk of major congenital malformations or birth defects. But they all have varying methodologies and differ with respect to some key features mainly infant follow up time, their malformation definitions, and availability of internal

comparators. And in fact the impact of these differing methodologies is evident when the birth defect rate for levetiracetam, which is an anti-epileptic drug, is shown across the registries. The monotherapy malformation rates for levetiracetam show tremendous variability with the UCB AED pregnancy registry representing a departure from the rest.

It was this very finding that has prompted us to seek a review from our colleagues at the North American Registry and at this point I would like to thank Dr. Holmes and Dr. Hernandez-Diaz for their thoughtful review. The objective of their review was to determine if the UCB AED Pregnancy Registry Birth Defects would have been included in the North American Registry based on their ALCM definitions. And their review concluded that approximately 50% of the birth defects in the UCB AED Pregnancy Registry would have been excluded from the North American Registry.

The interpretation of the results from

the UCB AED Pregnancy Registry is further challenged by the absence of an internal comparator. In fact for the European Registry and the North American Registry where an internal comparator is available there are no notable differences in the malformation rates for Levetiracetam compared to Lamotrigine. And it is for this very reason that UCB considers that registries with an appropriate internal comparator provide the optimal benefit risk insight.

So in conclusion variations in malformation rates observed across the pregnancy registry are difficult to interpret due to these methodological differences. And in fact publications often don't present substantial enough information to assess these methodological differences making the evaluation of the potential impact of these differences on malformation rate estimations challenging. An appropriate internal comparator is important in assessing benefit risk.

Also these results highlight the rule of large multi sponsored registries and the need for

methodological harmonization for broader contextualization of finding.

And lastly pregnancy registries should not be the sole source of pregnancy related benefit risk information. They should be viewed in the context of other pharmacovigilance and other external data sources.

I would like to acknowledge once again the patients and physicians who are contributing, the expert panel members and the CAR colleagues at the North American Registry for their great further review.

Thank you.

DR. SAHIN: Thank you. And will Speaker Number Four please step up to the podium and introduce yourself.

DR. DOAMEKPOR: Good afternoon. My name is Dr. Lauren Doamekpor and I am a Senior Fellow as the National Center for Health Research. Thank you for the option to speak today at this important meeting. Our non-profit center assesses scientific and medical data and provides objective

health information to providers, patients, and policymakers.

We recognize the vital importance of requiring post-market pregnancy registries. These registries will clearly provide information, important information to improve product labeling and also enable health care providers to better inform women about drugs or prescription drug use during pregnancy. Even when risks are uncertain data from these registries can provide valuable insight into the potential risks from exposure to drugs or biologics. It is incredibly important that pregnancy registries use a rigorous methodology and protocol to insure that the data is scientifically sound.

Our comments today address the need to insure an adequate sample size that is sufficiently diverse and also the need for a surveillance system for all marketed drugs used by women of child bearing age.

Pregnancy Exposure Registries tend to be too small and often have not included sufficient

numbers of racial and ethnic minorities. This lack of diversity is a problem for many studies submitted to the FDA but for pregnancy registries this problem may be particularly pronounced because of the way that women are recruited and enrolled. Enrolling women through physician offices for example may limit the number of participants from ethnic minority groups because some minority groups are less likely to have health insurance or to have regular prenatal care. The physicians that they see in emergency rooms or clinics may be less likely to participate in registries.

Successful recruitment of women of color will require new and creative strategies for recruiting patients. A carefully created plan is needed to recruit in community centers and urgent care centers; a continued partnership with Text for Baby and other social media platforms used by a diverse group of patients is also essential. Whenever possible enrolling women directly into registries independent of physicians may be

encouraged, this may allow for the inclusion of women earlier in pregnancy and may also facilitate follow up.

The biggest challenge is really obtaining information on a drug safety during pregnancy as quickly as possible after a new drug has been approved and is already on the market.

However registries are not required for all new drugs. The FDA should require pregnancy registries for all newly marketed drugs used by women of child bearing age. And the agency should also consider requiring pregnancy registries for some older drugs that are widely used during pregnancy where safety data may be lacking.

So conclusion it is really essential for pregnancy registries be founded on methodologically sound protocols in order to produce scientifically sound data for the safety of drug use during pregnancy. This will definitely help patients decide whether to take medication during pregnancy or not.

Thank you.

DR. SAHIN: Thank you. Will Speaker Number Five please step up to the podium and introduce yourself.

DR. ECKER: Good afternoon. My name is Jeff Ecker. And I'm a Maternal-Fetal Medicine Physician. Like Mike Green I practice high risk obstetrics at Massachusetts General Hospital in Boston where I am also a professor at Harvard Medical School.

But I am here today neither representing myself nor either of those institutions. Instead I offer comments on behalf of the American College of Obstetricians and Gynecologists representing over 50,000 members who provide health care for women. I am a fellow of ACOG and I serve as chair of the committee of obstetric practice in which role I have the pleasure of serving with liaisons from the drug and the device divisions of the FDA.

We enthusiastically support the agency's efforts to evaluate and advance efforts to determine the safety of drugs and biological products in pregnant women. And look forward to

updated guidance from this group.

Our support is founded in the dual beliefs that more research is needed regarding the effects of drugs in women and on women's health and that such research can be appropriately conducted.

Our committee on ethics of which I am a former chair supports the position that pregnancy and/or its possibility should be neither barriers nor excuses preventing these important studies.

My comments today will be focused on how to make these registries workable for frontline obstetricians.

Counseling women regarding the safety of medication in pregnancy is not an unusual task for folks like me. For 50% of women use at least one prescription medicine at some point during pregnancy. Both rising rates of chronic disease and rising average maternal age at conception argue that the use of prescription medicines during pregnancy will only increase in the years ahead. And yet less information is available to

guide women and their physicians than we would like.

Too often I search available databases only to find that data to inform an evaluation of risk is limited or missing. Not surprising given the fact that pregnant women are often specifically excluded from trials looking at the safety of drugs before approval.

To fill these gaps as already noted by this group, registries are of vital importance because they record the experiences of women who have either used medications before recognizing they were pregnant or who have used medications after they and their providers have deemed it best for a safe and healthy outcome to a pregnancy.

I want to emphasize as in concordance with ACOG's immunization expert working group that obtaining information of vaccines is a vital addition to information about medications and want to be sure that all our conversations going forward focus on a broad definition of medications and biologic materials.

Yet while pregnancy registries are important, an important first step, they have as this group has already acknowledged important limitations. It is imperative that as many pregnant women that are exposed to a particular drug or vaccine enroll in available registries and enroll as early as possible in pregnancy.

And yet another limitation of registries is that all too often in my experience women and providers either don't know that a particular registry exists or find their process for enrollment too cumbersome.

Having a readily accessible online clearing house for open registries will be a great help to busy clinicians who find their time occupied with many tasks. How embarrassing that until preparing these remarks I didn't know that such a clearinghouse in fact exists albeit buried deeply within the FDA website.

ACOG for its part will commit to featuring a link to this in its resources to members but we hope that the FDA in particular can

play an important role in promoting registries to those who prescribe for pregnant women who are not obstetricians: primary care physicians, midwifes, family practitioners, and others.

All including the FDA should do more, however, to connect providers and patients with registries. Connections to registries could be made and should be encouraged both when drugs are prescribed and dispensed. Increasingly, of course, prescriptions are not written but transmitted and meaningful use is encouraged by the Affordable Care Act places a premium on electronic prescribing systems. Such systems will often recognize that the patient for whom a particular medicine is prescribed is pregnant either because she is receiving a prenatal vitamin or because the prescription is generated from within an integrated electronic medical record in which such a diagnosis is already flagged or noted.

ACOG and FDA should encourage those who use these systems to prescribe or to dispense

medications to include notification when a pregnancy registry is open for a medication in question.

Ease of use also includes ease of access. And when prompted patients access registries their interface should be easy and online and not paper.

Thank you for letting us speak today on behalf of ACOG. We look forward to partnering with the FDA and promoting progress in this important matter.

Thanks.

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

MS. DUFFY: Good afternoon. My name is Siobhan Duffy. I am research scientist with United BioSource Corporation. Today I'd like to talk about recruitment strategies to improve location enrollment. Based on my working experience at United BioSource UBC has been designing and executing pregnancy exposure

registries for a number of years now.

These are the recruitment strategies described in the FDA's 2002 guidance document: announcements, personal mailings, exhibits at professional meetings and sponsors working together with FDA and other organizations.

I'll provide an overview of the advantages and disadvantages or each.

Prescribing information or product labeling is the foundation of educational initiatives. In fact 29 of the 58 medications listed on the FDA website have information about their registry within their prescribing information.

These educational materials such as brochures are a good method for direct health care professional awareness and patient recruitment. We've also seen these used in clinical studies. But there can be a hesitancy on the part of the sponsor because of the perception that you are promoting use of the drug in pregnancy and/or there is a misconception that there is a known

risk about use for the drug during pregnancy.

Use of the internet and the website is another method of direct prescriber awareness and patient recruitment; it provides educational material, registration information and registry contact information. But this seems like it's for a number of products a missed opportunity for patient recruitment for the reasons that I have described up here. Many are not written in lay person terms. They are difficult to navigate; difficult to find. They seem directed for health care professionals. And many of them don't have recognizable product or sponsor branding.

Journals and magazines provide general distribution of prescriber awareness information recruitment but they can be costly and there is no certainty that you are going to get to your targeted audience.

The health care professional letters are an option to reach out to a targeted audience of known prescribers or likely to prescribe. In our experience at United BioSource the letters have

resulted in almost a fourfold increase in calls to the registry center and a noticeable increase in the short amount of time in patient enrollment.

Exhibits at professional meetings provide an opportunity for face to face conversations with health care professionals but the clinician is away from their practice and they may be less likely to identify an appropriate patient when they return to their practice.

Collaborating with the FDA and other agencies may allow for greater access to targeted patient populations, facilitating enrollment of the comparator group and this can also lead to multi- sponsor registries. 23 of the products listed on the FDA website are part of a shared registry. One of the challenges with multi-sponsor registry is when there is a conflicting interest in the registry whether it is an FDA mandate or strictly researched based or otherwise.

Most pregnancy registry information tends to be focused on health care provider awareness but in UBC experience direct patient

recruitment is more effective. As discussed earlier today approximately half of the pregnancies in the United States are unintended. So there is also most likely a high amount of unintended exposures and the patient may or may not share with the prescribing physician that they became pregnant while they took the medication or share with the obstetrician that they were taking the medication when they became pregnant.

There is a need for more general public information about pregnancy exposure registries and their purpose. Increased understanding of pregnancy exposure registries may increase recognition and interest in specific pregnancy registries that use direct patient recruitment.

Thank you.

DR. SAHIN: Thank you. Will Speaker Number Seven please introduce yourself?

DR. ALLEN: Albert J. Allen, Ely Lilly & Company. And I am senior medical fellow for Bioethics in Pediatrics.

I want to start by thanking the FDA for

holding this meeting and for the work that you are doing on guidance. I think that it is important.

My focus as a child psychiatrist is often dealing with patients who have obviously been born to mothers and in some cases those mothers may have used medications. And I think it is important to recognize that pregnant women have health care needs like everyone else and so we really do value the opportunity to try and learn more about how can they use medications and hopefully have an appropriate benefit risk. So this is an important meeting.

Next slide. Sorry. I am not going to talk too much about design challenges because I think there has been a lot of discussion about this already. Concerns that we have at Lilly and these slides are based on information from a number of our drugs where we've had registries or attempted registries. The issue of registries introducing bias into the population that you are studying is one that has been noted and this is a concern in a number of different areas.

The issue in terms of limited ability to enroll women early in pregnancy can be particularly problematic especially for teratogenic factors as was noted in the first trimester challenges.

We will get to the limitations on patient enrollment in just a minute but one of the things that we have found is that because of the design in enrollment challenges it can often take decades to reach an adequate sample size to be able to draw any sort of conclusions. And this has been noted by a number of speakers is a problem in terms of being prepared for how to treat patients that are in front of you today. Having data 30 years from now doesn't help a whole lot.

So for us probably one of the major issues is the enrollment challenge. We are dealing with drugs that in some cases the medical conditions that the pregnant women suffer from are ones that they may be sensitive about making others aware of whether through a registry or

other situations.

As a psychiatrist in particular I have dealt with a number of women who putting their data or the fact that they are being treated for a psychiatric illness into a database is a concern for them. And that is an obvious barrier to recruitment.

There are limited incentives that are available for health care providers to participate in these; in many instances the desire to add to knowledge. But again you've got a long lag time before they actually see any results at the registries. So there is some question about how useful this is as an incentive to say that they are contributing to the knowledge that will help other patients that they may treat.

We have legal limits on the risk that impact health care provider participation. In some cases they're concerned about potential liabilities to themselves by participating in a registry. We have challenges in terms of the role that the industry or the company can do in terms

of making people aware of the registry. Again this is particularly an issue where we are concerned often about are we somehow promoting the drug off label or doing something that would infringe upon the promotional practices. And I would just echo the comment that was made earlier about the value of having some sort of guidance around those sorts of materials. What is appropriate material; what is not?

We have as noted limited recruitment incentives for the patient population and in some cases we have got a small patient population to begin with.

So there are alternative methods with registries. You could have a government approach such as the Danish Registry in Europe. EUROCAT is another approach. A disease state registry or multi-drug registry has a lot of attractiveness because it means not one company is making people aware of it so that you may have less promotional concerns. Hybrid registries are another option and then integrated health care system or hospital

system approach.

So we think that this is something that it is important to have cooperation and collaboration. We would encourage more incentives.

Thank you.

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

MS. JONES: Good afternoon. My name is Cynthia Jones. I'm a pharmaocoepidemiologist at Biogen Idec working in drug safety and benefit risk assessment.

Biogen Idec has several approved therapeutics for multiple sclerosis. For those of you who don't know multiple sclerosis is a disease that disproportionately affects women of child bearing age.

As a result of our work in multiple sclerosis we have extensive experience in pregnancy registries.

We have recently and successfully completed pregnancy registries for Avonex and

Tysabri and we are now enrolling patients for a pregnancy registry for Tecfidera. Additional pregnancy registries are planned for other products that are currently in filing or in review globally.

Because of this experience and lessons that we've learned we have two recommendations.

First we recommend that the FDA allow greater flexibility in pregnancy registry protocols and not be specifying a comparative population. Better comparative population data than that which was pre-specified will become available over the life of the registry; for example the aforementioned Tecfidera registry which is currently enrolling is scheduled to be completed in approximately eight years. The availability of population based MS background rates and other informative external sources may greatly evolve over the course of those eight years. It could also be considered premature to a priori select external comparison groups prior to knowing the demographic composition of the

registry patients.

Therefore we recommend that the FDA in the guidance allow flexibility in the protocol and not be specifying a comparative population.

Second we would like to see the FDA facilitate birth outcome data. We find great potential value in the use of data such as that provided by the Medication Exposure in Pregnancy Risk Evaluation Program (MEPREP). We believe that coupled with existing background data, programs such as MEPREP could provide another source of comparative data on many different disease states and medicine use patterns.

In summary based on our extensive experience in pregnancy registries and anticipation of more registries into the future we have two recommendations: One, flexibility in FDA guidance regarding protocol design and not forcing a priori comparative populations; and two, FDA facilitated availability of additional comparator data.

Thank you.

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

MS. RYAN: Hi. I am Kate Ryan. I am with the National Women's Health Network. It is an advocacy organization networks to improve the health of all women. We bring the voices of women consumers to policy and regulatory decision making bodies. And we are a membership based organization. And do not take financial contributions from drug companies, medical device manufacturers, insurance companies or any other entity with a financial stake in women's health decision making.

The network has long advocated for the FDA to provide better information for women about the safety of drugs used during pregnancy both provider recommended and guided as well as accidental exposure. So we are very pleased that the FDA and the FDA Office of Women's Health in particular has convened this meeting to discuss how to evaluate the safety of drugs and biological

products used during pregnancy.

I am going to bring the patient perspective today as I said we are a membership based organization and let the trial design of registries, leave that up to researchers.

What I want to say for women, so pregnant women have historically been excluded from most research trials due to the concern that trial participation could harm the fetus even from research that would advance our knowledge of medical conditions and treatments intended to be used during pregnancy. As a result we don't have nearly enough information to provide women with accurate information which is particularly disturbing when you consider that more than half the pregnant women take at least one prescription drug during pregnancy.

I am not going to go into detail today about this particular topic. But I do want to find a way to include pregnant women in more research because it is an important part of this larger conversation kind of with the exception of

what we've already seen so recently a drug approved for nausea and vomiting during pregnancy that actually did the type of thing we want to see which is to study the women it is going to be used in.

As a national membership based organization the network hears women across the country looking for information about drugs and medical devices and procedures. We believe that with the right information every woman could make a good decision about their health care.

Our Women's Health Voice which is a health information clearinghouse that we have hosted since the '70s provides women with evidence based information about medical products and procedures so that they have the tools they need to be an active participant in their health care with their provider.

We strongly support the inclusion of women in more clinical trials and post market studies including pregnant women.

Without an adequate research

infrastructure that can provide this type of evidence based information we really can't give women the information they want and need. About a year and a half ago I spoke at an FDA Advisory Committee Meeting about the use of Teratogenic drugs by women of reproductive age and potential pregnancy exposures, a topic with obvious connections to the focus of today's meeting. As I had said then the network believes that the FDA should not restrict access to an effective medication because of women's reproductive capacity but at the same time we have to support the collection of data through registries to track what happens in the event of a medication exposure during pregnancy. The long term data collected from registries and other long term studies can provide important additional information about the safety of a drug beyond what we can get from a short term pre-market clinical trial.

I know they can be difficult to enroll women and we've heard today that it can be difficult to enroll women in pregnancy registries.

You know there are typically high dropout rates and poor follow-up. However, we have learned from a successful community based participatory research in other areas that people and women in particular are more likely to enroll in and remain in engaged in a trial or research if they feel engaged in the research. And somebody had spoken to that earlier today, one of the panelists. But it essentially means that health care providers with patients who become pregnant while taking a drug should be having conversations with their patients about the purpose and public health value of the research to insure they understand the option of enrollment as well as the benefits of enrollment not just to themselves but to the public at large.

And additionally what we've seen is when the FDA research and providers share the study results when they become available women feel more positively towards their participation in the research. It is not enough to conduct the research. However, women and providers do depend

on the FDA to provide them with clear, accurate, and timely information about what has been learned from the research of affects of drug used during pregnancy.

But until the agency follows through with the commitment to release the guidance for industry on drug labeling pregnancy categories we are going to have a bit of a disconnect. We really urge the FDA to finalize and release this long awaited update to the guidance on pregnancy and lactation labeling.

We also recommend the FDA work with women's health organizations and women's health providers to insure the information is communicated in consumer friendly language so that when women get the information they can understand it and use it to make a decision that is based on their own priorities, concerns, and values.

Thank you very much.

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

DR. CLOWSE: I am number 10.

DR. SAHIN: Okay. Sorry. Ten.

DR. CLOWSE: I am going to keep going. I am Dr. Megan Clowse and I am Rheumatologist at Duke University Medical Center. I am also the Director of the Duke Autoimmunity and Pregnancy Registry which includes now about 300 patients with various Rheumatologic ailments in pregnancy.

I wanted to raise what I think is an important topic that has not been discussed yet today much which is the impact that disease activity has on pregnancy outcomes and how that can particularly influence how we interpret the data about pregnancy outcomes with medications.

So we know that in many diseases in my world certainly Lupus in other world's things like diabetes and inflammatory bowel disease that having more disease activity during pregnancy leads to worse pregnancy outcomes including more preterm birth, more pregnancy loss, lower birth weights, et cetera.

And so it is important that when we look

at the medications that these patients are taking they really take into account how much disease activity they have and how that is leading to their medication use. So for example in Lupus our patients who have a history or active Lupus during pregnancy will be on more drugs than our patients with Quiescent Lupus and, therefore, will likely have more pregnancy outcome problems potentially because of their disease activity or potentially because of the medications and it really makes it difficult to kind of tease out those two problems.

I think that it's particularly important when we look at what control groups we use. So we need to have some control groups that are probably matched in their disease activity level to the patients who are on the medications. And I think it makes healthy controls often not a great control group for our patients with chronic diseases. So a patient with Lupus who comes into a pregnancy is just at much higher risk for pregnancy complications than a healthy woman. And that doesn't necessarily have anything to do with

the medications that she takes. It is just who she is. And we can't modify that she has Lupus or not. What we can do is with the medications.

So I just want to add that I think that it is really important that disease activity measures be included in these registries figuring out how to collect that information I think is a significant challenge. Getting that data from physicians I think would be probably the most valuable but also probably the most technically difficult. And I think that we all know that physicians, myself included, are often not the most receptive and responsive to more questionnaires. But I think that there are new and evolving patient reported outcomes as well that can be useful and might be able to at least give the investigators a general idea about a patient's disease activity and, therefore, be able to use that as I understand medication toxicities.

Thank you.

DR. SAHIN: Thank you. This concludes our open public comment session. Thank you for

everybody's participation.

MS. MOYER: So we are ready to start our next topic. And Pamela Scott will lead us through the afternoon.

DR. SCOTT: Welcome to the afternoon session. And we are going to start with some introductions since we have two new panelists joining us. So we are going to start by asking Kim Thomas and Julia Beck to do a brief introduction. So we will start with Kim Thomas.

MS. THOMAS: Hi. My name is Kimberly Thomas. I am a Senior Public Health Advisor in the Office of Women's Health and I focus on health communication and outreach activities.

MS. BECK: Hi. My name is Julia Beck. I am here as a lay person. My day job actually is running an organization called Forty Weeks where we focus on helping brands to connect with new and expectant parents. Our clients include Madilla, Bravado and others focused on helping make that transition a positive one. But today I am here as a patient, as somebody who participated twice in

pregnancy registries, one in each century actually.

[Laughter.]

MS. BECK: Tah-dah.

DR. SCOTT: Thank you. And welcome.

So the afternoon session is going to focus on issues related to enrollment, retention and communication of pregnancy registries. In the morning sessions we learned that pregnancy registries are a valuable tool to collect data to examine the risks of medical product exposures during pregnancy. As we discussed in the morning presentations pregnancy registry data can inform product labeling and clinical practice guidelines.

During the course of the meeting today we discussed the challenges related to data collection analysis and briefly touched upon issues related to enrollment, retention and communication.

Now for this afternoon session we want to shift gears a little bit and have a more in depth discussion as it relates to these issues.

And our first speaker today is going to be Kimberly Thomas. And she is going to talk about the use of digital outreach and innovative partnerships to raise awareness about the pregnancy exposure registries.

MS. THOMAS: I am short so I need to lower the microphone. I am just going to share with you today some of the digital outreach and educational partnership strategies that we've used in the Office of Women's Health to help to raise awareness about pregnancy exposure registries amongst women as well as amongst health professionals.

First let me just give you a brief overview of the Office of Women's Health. The office was established in '94 with a mission to protect and advance the health of women through policy, science and outreach. And in support of our mission one of our main focuses is to translate and disseminate FDA information to the public. And that is the role that we take in terms of pregnancy registries.

Now our outreach program really centers around our Take Time to Care Program which is an umbrella initiative for all of our consumer outreach activities. We target consumers directly but we also go through health professionals and other community decision makers and advocates who reach women in a variety of roles that they have in their lives.

We do partnerships with a variety of different types of organizations. And we conduct outreach campaigns as well as digital outreach including videos, website and social media, some of which I'll talk about today.

Our outreach program uses five main strategies or components to reach our target audiences. We have consumer education, campaigns, partnerships, conference exhibits, and presentations to target the health professionals as well as electronic outreach, everything from social media to the FDA website and our technical assistance.

Now our pregnancy initiatives really are

in three main areas: the pregnancy registries webpage which we've heard a lot about today, our consumer education and outreach, and our health professional outreach.

Now let me start with the pregnancy registry page since we've already heard a lot about the information that is on the page I am going to talk a little bit more about why it was created and what we've done to try to improve the page over the years.

Now initially we heard from our stakeholders that it was hard for women and clinicians to find the contact information for registries You had to go on an individual basis, go from one site to another. They wanted a one-stop shop. So the page was created about ten years ago to connect consumers and health professionals to the registry information and just to raise general awareness about pregnancy registries.

Now this is the website which you've seen earlier today. In 2011 the Office of Women's

Health conducted some usability testing in an effort to learn more about how the public get their feedback about the website and try to improve its functionality. Now usability testing provides an opportunity to use a small sample of your potential website users to gain feedback about how easy it is for individuals to find information on the website and to get their general feedback about the types of information they are looking for.

Our testing, we were trying to figure out how health care providers and consumers found information on medication and pregnancy on the FDA website and to identify the resources that they use in addition to FDA to get information.

We used a sample of 16 participants, eight consumers and eight health care professionals and we were really trying to target a representative sample, different ethnicities, different professional backgrounds within the D.C. area to get their feedback. And they conducted some timed tests in trying to find basic

information and they also gave us feedback on the different sections of the site.

The first thing that we learned from the usability testing was simple. Few people think to go to FDA to our website. Most have never used the site at all. And the providers were more likely to go to other sources like other government websites, the drug companies, clinical studies, the literature, drug reference books; everything but FDA.

The women really what we learned from the conversations and from their tests was that they were heavily influenced by their primary care physician or their OB/GYN when it came to getting information. But one of the things we also learned was that women definitely used the internet to search for information about the drugs that we are taking.

In this testing we didn't go into detail about the quality of the information but there is a separate FDA paper that was done with some of our external colleagues that talks about the lack

of evidence for some of the sites that these women go to.

One of the other things that we learned was that something that we already kind of knew about the website that both health care providers and consumers had difficulty finding the information about pregnancy and medication use. Many of them had to go through many clicks before they actually got to the site. Those who did put pregnancy in the search box were able to find the listing as well as find our other consumer information.

And I just need to note that this testing in 2011 was done before the FDA did the latest round of upgrades to the website. So things have changed considerably since the testing was done.

When the women got to the pregnancy page they found the information useful but they gave us some insight into the problems that we may have in terms of communicating with the public about pregnancy registries. They didn't find the name

intuitive and if they saw it, it wouldn't catch their attention as something they would want to click on.

We also found some interesting information from the consumers about what they were looking for. Many of the consumers wanted more information on how the registries worked and what they would need to do when they participate. There was a link there but we decided to upgrade the information to really try to allay some of their fears.

And we also found that the health care professionals wanted more direct information, links to the drug label and that type of thing.

For us what we decided to do in 2011 was to do more direct outreach related to pregnancy registries. We wanted to promote the existence of registries and the benefits of the registries not only to the health care professionals but to the women as well. And we wanted to provide more general information to allay women's concerns and fears about registries but just to also provide

some general education.

Some of the challenges that we faced was the feedback that we got kind of mirrored some of the comments we had from earlier today about women really wanting more definitive answers right now. And being able to educate them that pregnancy registries wouldn't provide that information but it could be a valuable tool for them if they had future pregnancies but also in their role to help other women.

Our response was to develop some digital outreach strategies as well as some partnerships to increase our education related to pregnancy registries. For our digital outreach we definitely did some direct updates to the pregnancy registry web pages, we added pages, we tried to make the navigation more user friendly and we also upgraded our pregnancy topics page which includes links not just to the pregnancy registries but to other FDA content for pregnant women.

We started doing more website features

and spotlights. And we also developed some new tools, website cards as well as web buttons that we could promote to our partners to try to raise awareness about pregnancy registries and about the website. And we also expanded our Twitter outreach.

This is just a screen shot of the pregnancy topics page that includes the links to the registries as well as some of our other information.

In addition to the digital outreach we started some new partnerships. In 2012 text4baby came to us because they had seen some of the previous video outreach that we had done to Hispanic women. They were interested in expanding their outreach to African American and Latino women. And we were interested in doing the same in terms of pregnancy registries. So as a result we joined forces to develop a short video in English and Spanish that was launched in May of last year to educate women about medicines in pregnancy, about the resources available through

our pregnancy website, and also to let them know about the existence of pregnancy registries.

We did a lot of different types of outreach including our stakeholder outreach, our social media, and our YouTube Video ad campaigns. All of these were successful and they are ongoing. This was just the first step in our attempt to really start reaching out to diverse audiences about pregnancy registries.

This is screen shots to show you some of the flyers that we used to promote the videos in both English and in Spanish.

In addition we have a whole portfolio of educational materials that are written in plain language for women. We've been distributing our materials for years. But in December of 2012 we launched a special pregnancy publication promotion to make available our materials on pregnancy registries, our fact sheets on medicine in pregnancy as well as some consumer updates from the FDA Office of Communication that are designed to educate the public about pregnancy registries

and medicine in pregnancy.

Now we've distributed over 800,000 publications and these materials were made available in bulk to health professionals to community based organizations as well as national associations.

And this slide shows some of the materials that are available, our tear pads, the website cards, and our fact sheets.

Some of our other partnerships were designed to really raise awareness about the website and to encourage both consumers and health professionals to access our print and online publications. We partnered with USDA to reach out to over 4500 WIC agencies across the country to make information about pregnancy registries and our medicine in pregnancy fact sheets available. We also work with the HHS minority health resource center to distribute the medicine in pregnancy and pregnancy registries materials through their call center and through their preconception health initiative.

And lastly OWH provided funding to FDA's public affairs specialist, our field staff, who do local and regional outreach throughout the U.S. and Puerto Rico to make the materials available in those areas as well.

Our health professional outreach was really in two different forms. We did our traditional conference outreach in stakeholder meetings where we tried to raise awareness about the website and about the materials that are available for health professionals. But also as a part of a partnership that was already ongoing in the Office of Women's Health to develop a woman's health curriculum and tool kit for schools of pharmacy, we made sure that information on the pregnancy registries was included in the resources so that those training students would have access to that information early and would begin to incorporate in their practicum training and in their future practice.

And lastly we make the materials available to health professionals through our

interagency projects such as the partnership that we sponsored for several years with HRSA in their clinical pharmacy services collaborative that provided clinical pharmacy services to women at HRSA funded clinics and community health centers across the country.

This last slide is just to show you a little bit of some of the outcomes. These are some of the milestones in terms of our web traffic. It is just the beginning. We are the FDA so we don't have millions of visitors the way some other websites would. But we are hoping that the feedback that we get from this meeting will help us to ramp up our outreach digitally and in terms of our partnerships.

And I will just end with a slide that shows you some of our resources that we have available.

And that is it. Thank you.

[Applause.]

DR. SCOTT: So we are going to open it now to questions from the panel to Kim. Are there

any questions from the panel?

Okay. So we will go on to the next speaker. The next speaker is Dr. Cristina Chambers and she is going to give her perspective from the Teratogen Information Service. Dr. Chambers is a professor of pediatrics from the University of California, San Diego and also a member of the Organization of Teratology Information Specialists Collaborative Research Group.

MS. CHAMBERS: Thank you. So I am going to talk about recruitment, retention and communication from the OTIS Mother to Baby Pregnancy Studies perspective.

And this is the various companies which we receive research funding from for the studies that we do.

For those -- I think most of you in the room probably know something about the Organization of Teratology Information Specialists. Now with our more consumer-friendly name Mother to Baby Services. The first service was established in the late '70s. And in the mid

'80s we formed a network of these services that covers the U.S. and Canada with about 13 active sites in the U.S. and Canada that are part of the network for providing service.

We provide toll free typically telephone information to pregnant women and health care providers regarding the safety of medications and other exposures, vaccines and chemicals and occupational exposures and infections and so on during pregnancy and breast feeding. And this is done on a national routing system basis so that a woman who lives in a state where there isn't a service can be routed to a service where she can get that information or a provider as well. We respond to approximately 80,000 to 100,000 contacts via phone or other methods each year in English, Spanish or French.

The newest service was just added last year in 2013 so we are happy to see the group growing and this is the Mother to Baby Georgia services that opened in Atlanta at Emory University and provides service to the State of

Georgia.

Mother to Baby pregnancy registries conducted by the Organization of Teratology Information Specialists are conducted in one way through the OTIS research center, a collaborative research center that was established at UC San Diego in 1998 initially with the ARAVA Pregnancy Registry and we currently conduct U.S. and Canada wide cohort studies that meet pregnancy registry commitments or requirements.

And we also conduct the cohort arm of the Vaccines and Medications in Pregnancy Surveillance System or VAMPSS in collaboration with the American Academy of Allergy, Asthma and Immunology and the Slone Epidemiology Center of Boston University. And you will hear some more about that tomorrow from Alan Mitchell.

The basic design of the Mother to Baby Pregnancy Registries is shown on this slide. So in terms of recruitment what we do is have individuals or services or sponsors or other methods whereby a provider or a pregnant patient

or a person planning pregnancy is referred into the OTIS research center. And those -- a variety of referral sources hear about the studies that we are conducting and if a patient or provider has a patient who might qualify or be interested in participating in the study we require that the mother herself be the person who is ultimately routed to the research center. And at that point she is screened by trained interviewers who determine if she qualifies for one or more studies that we're conducting. And then in turn determines if she is willing to participate in that study.

And if she agrees to participate she can be recruited typically into one of three cohorts, a group of women who have taken the medication or received the vaccine of interest some time during pregnancy and meet the recruitment criteria for that cohort. If it is a medication used to treat a disease we typically have a disease matched comparison cohort where women are recruited who have the same underlying disease or diseases but

have not taken the medication of interest. And then we typically have a healthy comparison group of women who contact, typically these come through the Mother to Baby Services so women who don't have the disease or haven't taken the medication or haven't received the vaccine but are recruited in the same manner followed in the same manner as the other two groups throughout pregnancy.

Women in all three groups participate in multiple maternal interviews that take place up to four times during pregnancy. If there are underlying diseases involved we typically do have an assessment at least two time points during pregnancy of disease activity or disease severity.

And then all women in each of the groups are followed through the outcome of pregnancy and an outcome interview is conducted. Medical records are requested and reviewed. And the standard is that the children, live-born infants, are followed up to one year. For some studies the follow up is as long as five years. And for many of the studies depending on the drug or disease we

also have incorporated a specialized physical examination by one of the study pediatricians, geneticists, who actually travel to see the live-born children wherever they live in the U.S. or Canada and infant photographs are taken in those cases as well.

The recruitment strategies that we've used, many of these have already been mentioned, ones that target both patients and providers are, and of course we rely heavily on spontaneous callers to Mother to Baby Services. And we also ask those services to do outreach in their catchment areas so that they contact providers, clinics, locations where potential participants might be identified and referred who might not otherwise contact a service.

And we have identified some additional clinical referral sites that aren't locations of Mother to Baby Services where pregnant women are seen, either high risk or routine OB care and they proactively refer to us as well.

We ask Pharma sponsors for various

studies if they receive contacts from pregnant patients or providers with the exposure of interest through medical information or safety or through their medical liaisons that they refer to us as well.

We recruit through our website, through the FDA Office of Women's Health website, Clinicaltrials.gov, and we provide marketing materials, brochures and so on for providers but also posters and brochures that appeal directly to consumers that providers can distribute in their offices.

And we are using, and I will talk about this in the next slide or two, on a pilot basis an electronic medical record best practice alert mechanism for obtaining and facilitating referrals from obstetricians.

We also recruit through Mother to Baby fact sheets which are simple two-page two-sided question and answer descriptions of what is known about a particular drug or a disease in pregnancy. And we produce those across the network and post

them on the website. And make sure when we have a new drug under study that we produce a fact sheet for that drug and those are heavily downloaded from the website. And each one of those has the contact information for the pregnancy registry.

We also receive contacts from providers and patients where the patient is not yet pregnant so maybe planning pregnancy or considering pregnancy and she may wish to enroll in a future pregnancy and so as part of the Mother to Baby Registry those patients are tracked and if they give permission we re-contact them to see if they do become pregnant.

I mentioned the fact sheets. This is just a screen shot of the website that shows the beginning of the list of fact sheets that are available in English and Spanish and some in French and as I said are heavily downloaded in our source of recruitment for pregnancy registries.

And then I mentioned our pilot basically because we are doing this at UCSD through the electronic medical records system that exists

there in reproductive medicine. And what we did was initiate a best practice alert in the EMR so that when the obstetrician sees a patient for a prenatal care visit he or she gets a best practice alert saying this patient may benefit from receiving counseling about the medications or other exposures that they have had or may have in pregnancy. And if the physician accepts then we automatically get that referral to our Mother to Baby Service. And the patient also on the patient visit summary gets a printout that indicates that they have been referred to the Mother to Baby Service. And the clinician has an opportunity to explain to the patient why they have made this referral.

We then in turn contact the patient so that gives us permission to contact the patient without having to wait for them to contact us to provide them information about any exposures that they may have had and also to determine if they would be interested in or qualify for participating in a study. And the information

that's provided to the patient is then summarized and put back in to the EMR so that the provider when they next see the patient can see what the summary of that encounter was.

And we've expanded this a little bit in the last year to see if this sort of mechanism would work with women of reproductive age who are not pregnant but who have the potential to become pregnant. So we have piloted this in Family Medicine, expanding it to Internal Medicine and Adolescent Medicine where the best practice alert comes up on the basis of a prescription that is being written or refilled for a woman of reproductive age where the drug is a known human Teratogen but certainly has the potential for being more broadly instituted for medications or vaccines that are under study for pregnancy registry. And that has been successful in our local setting as well.

So the variety of types of locations where Mother to Baby Services are located and our active referral sites includes primarily OB/GYN,

pediatrics and genetics departments in university or hospital or department of health settings. The active clinical referral sites that are not Mother to Baby Service locations are Georgetown University, University of New Mexico, Kaiser Southern California and we are just establishing a new clinical referral site at University of British Columbia.

Recruitment strategies that are specifically targeted to providers over and above the ones I just mentioned include professional print media which we think is pretty much a waste of time and money. We do professional organization emails to members of these professional organizations and website information. And this is particularly facilitated by the American Academy of Allergy, Asthma and Immunology to their professional members.

We do quite frequently direct mailings to physicians and other providers who see the patients that we are targeting for recruitment to give them updates on the study, provide them with

brochures and let them know that we are still interested in referrals of patients.

We do the exhibits at multiple professional meetings and present abstracts as appropriate. The contact information, of course, is typically in the pregnancy label. And then resources that professionals use like Briggs, Drugs in Pregnancy and Lactation and Reprotox will typically list the pregnancy contact information for the registry in that drug monograph.

And then the Mother to Baby website is also used or provides an opportunity for providers to refer via the website a patient without having to try to find the phone number and try to contact us. They can do this using a secure referral mechanism via the web.

For patients over and above the strategies I just described we also do extensive paid print, web and radio advertising on heavily used sites like Babycenter.com, advertise in Pregnancy and Newborn Magazine, we get some unpaid

media coverage through distributing press releases and other types of coverage. We partner with agencies such as WIC to disseminate information about pregnancy registries. And we partner with patient supported advocacy groups and professional practice groups, so the Crohn's and Colitis Foundation is in an active partnership with us now to proactively recruit through their database, National Psoriasis Foundation and so on.

We also do direct to consumer recruitment through the Mother to Baby website and through social media such as Facebook, Pinterest, Google ads and so on. And this is an example of the website that is patient focused that describes the studies that we are doing and includes a page that also tells the potential participant what it means to participate in the pregnancy registry and what the benefit might be and how it might help others in the future.

And this is a screen shot of the Facebook page with about 10,000 fans and this is our newly launched Pinterest page.

The challenges and barriers to recruitment, some of these have already been mentioned. Certainly for providers we think the biggest barrier is knowing and remembering when, where and how to make a referral. So specialty physicians may not often see a pregnant patient and OB/GYNs may not often see a patient who is exposed to the target medication or the vaccine. So playing both sides of those barriers is a challenge.

For patients it is the same thing; knowing that the study exists is the major barrier if their provider tells them or not or if they hear about it on the internet. And certainly as we have heard before this certainly can affect diversity and may contribute to a selection bias in terms of those who do know that the study does exist and then in turn enroll.

Following through on a referral if the provider does make the referral is an issue as well, a barrier to recruitment because we know that there is a big gap between the referral being

made and the woman actually taking the initiative to make the phone call and contact the registry. So we do everything we can to try to encourage that the provider obtains permission for us to contact the patient rather than asking the patient to initiate the contact.

We survey women who come to us who have qualified for the study or appear to qualify but decline to participate and ask them if they will provide us the reasons why. And the two top reasons are time needed to participate and reluctance to release medical records which we heard earlier today.

The time needed to participate I think we need to learn a little bit more about that because it is not a defined response. So we don't know whether the objection is that over the course of pregnancy this is going to take three hours of their time and they would be okay if it took 90 minutes of their time or if it is just that it seems like it is an overwhelming thing to take on when you are already dealing with a pregnancy and

everything else in life.

The reluctance to release medical records I think is a real concern and is something that we have seen I think increase over the years in terms of that being stated as a reason for not wanting to participate.

In terms of retention, the second topic, I think we are lucky that once we get a person enrolled in the study that we've had really great experience of all the various studies that we've enrolled participants in through this process over the years. Our losses to follow up have averaged five percent or less. It certainly varies from study to study and varies depending on which group the woman is in but overall our loss to follow up rates have been quite low.

And we attribute this to a number of different factors but the primary thing we think as has been mentioned before is that mothers are always the enrolled registry participants and that is important for scientific reasons in terms of getting accurate exposure information. But we

think that having the mothers as the individual who is enrolled in the registry makes a huge difference in terms of retention.

As we mentioned we do up to four telephone interviews during pregnancy and so there is a relatively short interval between participant contacts. So we develop sort of a frequent interaction with the participants which we think aids in retention. Women who are enrolled with us have ready access to Mother to Baby counseling services. So as their pregnancy progresses if they have a question about an antibiotic they have to take or they just you know sprayed their house for fleas or whatever they know they can call and get information about that exposure and have sort of their personal counselor available.

We think that rapport does develop between the participant and the study interviewer over the course of the pregnancy and in the at least one year follow up. And we try to make it as easy as possible for participants so not hounding them with phone calls to set up a

telephone interview. We try to offer alternative methods of contacting them via email or text to set up appointments to call.

Other retention strategies ones that are used in epidemiologic studies all the time that we have tried to get multiple other family and friends contact information in case the participant can't be located.

We staff to allow as best we can interviewers to contact participants outside of regular business hours, evenings or sometimes even weekends. And we are testing opportunities to offer alternative methods for some data collection. So our interviews sometimes can be depending on how many exposures the woman has in her history can be 45 minutes long. So we are testing in one situation now doing an additional asthma survey where the mother is offered the opportunity to be able to complete the survey at the tail end of the telephone interview or she can opt to do it via secure web process. And so we will look to see what's the uptake in terms of

opting for the secure web survey and then how many of those are completed from among those who accept them.

The physical examination of live-born infants although it certainly has some important scientific advantages it is labor intensive and expensive but we think it serves as a retention strategy as well that patient's families really look forward to this and anticipate it when it takes place in the first year of life and they look forward to the feedback that they receive from the exam.

And a much more remote retention strategy is study results which as we all know don't come around as quickly as we would like but publications are sent to participants as sort of a concrete evidence of what their participation produced.

Challenges and barriers to retention primarily the time burden for pregnant women and new mothers to complete all the parts of a study. And this is true on one end of the spectrum for

very complicated pregnancies where the women are just overwhelmed. And then I think on the other end of the spectrum too for very uncomplicated pregnancies for example unexposed healthy comparison pregnancies where maybe the motivation wanes over time to complete study participation.

I don't know whether this plays a role in retention but we have not typically used participant monetary incentives. The rationale for women enrolling in the study is altruistic by and large. But it is something that is worth testing.

Communication strategies and this has been discussed a lot earlier today that communication to providers is greatly simplified if the registry design is disease based. So even though we really don't have a disease based registry for example for autoimmune diseases we have a series of pregnancy registries that really as a group comprise a multiple disease based registry.

We try to spin this so that providers

see it as a disease based registry and so rather than them having to think does my patient take this drug or that drug for this disease that they are encouraged to refer patients who have the disease regardless of the medications that they are using to treat that condition. And this simplifies greatly knowing who to refer. It certainly encourages referral of patients who qualify for that disease match comparison group. And as a side benefit of this it adds important knowledge about the contribution of the disease to pregnancy outcomes as was mentioned by one of those who made public comments.

In terms of communications to patients and providers about the existence of the registry we think this is facilitated by the use of one contact number. It certainly would be optimum if pregnancy registries involved one contact number period. But certainly for the ones that we do we utilize the same toll free number since 1998 and we think that that helps with communication.

Just as an example of one of the side

benefits of doing something that is ultimately a disease based registry we've been able to produce some information about factors that contribute to adverse pregnancy outcomes in women with an underlying condition for which we are studying multiple medications used to treat that condition.

Challenges and barriers to communication this again has been discussed. We struggled with this issue but for scientific reasons generally speaking the release of data in Mother to Baby studies with consultation of the advisors is typically held until the end of the study or time point at which a formal analysis can be conducted. And this is driven of course by sample size either requirements or having met a sample size that the advisors and the investigators agree meets the objectives of the study to the extent that they can be met and allows adjusted analyses. So this in turn, of course, can lead to time delay in availability of final results for some registries depending on how often the product is used and if it is infrequently used by pregnant women it can

delay release of information of the final study results for a longer period of time.

So in terms of future directions I wanted to mention a couple of things about addressing recruitment challenges which I think are the major issue at least for our pregnancy registries. We think that this facilitated referrals through electronic medical records best practice alerts our experience has been that this works and that its I believe a huge benefit for clinicians and could certainly be expanded across many, many settings where EMR regardless of what the proprietary product is can easily be adapted to do this.

In terms of women who decline because of lack of time or reluctance to release medical records we've considered the possibility of offering a two tiered level of participation so that women who would not enroll because they don't want to spend the time or release medical records but might be willing to enroll if they could do one interview and one outcome interview and didn't

have to release medical records; would that be worthwhile? So is that information gained that we would otherwise miss certainly introduces complexities into the analysis and the sample size.

And then we are testing the impact of monetary incentives in a new study that we are taking on to see if there is evidence for an increased participation rate; is there evidence for increased diversity in women who enroll in the study based on the incentives. An important flip side of that is does it negatively impact retention. So if women would not otherwise enroll if they didn't have the incentive; does the incentive keep them in the study as well?

And then finally we would like to increase electronic patient driven collection of selected data that we think can be reliably collected and validly collected using methods such as a participant's personal web portal for some information that we now spend time on the telephone collecting or we ask the participant to

complete on paper such as the pregnancy diary.

We'll end there. Thank you.

[Applause.]

DR. SCOTT: So are there any clarifying questions from the panel for Dr. Chambers? Trinka.

MS. COSTER: Yeah. Listening to this I was just you know all of a sudden I became aware of actually holding records and I haven't heard anybody say like and then when do you destroy them. And then the second question I presume you have all the HIPAA requirements so if you release or if you are hacked in then you have to notify everybody and tell them about that that their personal information has been released. So same rules and --

MS. CHAMBERS: Right. Right. Diana could tell you way more the specifics but yes medical records, we consent participants to the retention of medical records indefinitely and we have a whole separate HIPAA consent process that goes along with consenting into the study for both

the mother and the child. And yes the set of rules that go along with that about protection of privacy.

MS. BELINER: Can you explain more about the EMR thing that you are doing. So I think I heard you say that the doctor asks the patient if they want counseling. And then if a patient agrees then you transfer the patient's information so is that all HIPPA compliant. And then also well answer that one.

MS. CHAMBERS: Yes. And it is partly because we are in the same institution that that was easier to do. So we are in the same covered entity. And the consultation that the provider is asking for is for us to provide information to their patient about any of the exposures that their patient has had. So the trouble we have with clinicians is you know they go through the list and they say well maybe she needs to know about this or maybe she needs to know about that. So I think that they are thrilled with having the opportunity to just say you talk to them to figure

out what it is that they need to hear about, provide us back with the information because they don't want to be left out of the loop. They want to know what we told them so they can then act on it or follow up on it. But that also works well for us just like it does if somebody comes in from a provider referred over the telephone from another institution; it works well for us to then be able to say after we've provided the counseling, would you be interested in hearing about some of the research projects that we do.

That system doesn't necessarily have to work that way. And actually the way that I described it for non-pregnant women but who have the potential to become pregnant, it can be set up so it specifically targets you know the 50 drugs that you are interested in looking at and the alert only comes up for those. And then that alert can make the referral specifically to hear about a pregnancy study if the patient accepts; and if the patient accepts, then it is a done deal. So it works beautifully. And there really isn't any

reason other than getting beyond whatever the firewalls are and doing this with Kaiser or doing it elsewhere that it couldn't work other places at least in my opinion.

MS. BERLINER: No I think it is interesting because one of the public commenters also mentioned something about linking the registries to the EMR systems. And so do you know how many of your referrals come through that way versus all the other ways that you've talked about?

MS. CHAMBERS: It works beautifully for common exposures like vaccines; so lovely if you know 20 to 50% of women are receiving a vaccine. It works for less common exposures. For something that is an extremely rare exposure say for example at our institution if there are 5,000 pregnancies a year, the likelihood that we are going to come up with very many exposures to one category X drug that is used by .001 percent of pregnant women is low. But for something that falls in the mid like for psychiatric medications, for things, asthma

medications it works quite beautifully.

DR. SAHIN: So this morning Dr. Holmes had presented data where he showed that when there is a physical examination done by one physician that the outcome -- that the malformation rates are different than when you look at medical records. So have you had the same experience with your dysmorphologist doing the examinations of all the infants compared to your studies where you get medical records?

MS. CHAMBERS: So that is a really good question. And I think Lou Holmes is the inventor of that topic. I think and Diana can speak to this. The major value and why we include the physical examination is with small sample sizes to be able to say that we've had this careful evaluation of children to look at whether or not there is a specific pattern of minor malformations which are completely unreliably abstracted or recorded in medical records. And so to do that requires the physical examination in a blinded fashion by a study trained pediatrician; and that

is the major purpose of it.

As a an additional benefit it certainly is a mechanism whereby we can validate that if the child does have a major malformation that is the one that the pediatrician or whoever the health care provider is says that the baby has.

And there is and Diana can say -- I mean there is the odd situation where it turns out that the diagnosis was wrong by the local pediatrician and that is part of the engagement with the parent that the pediatrician then goes over this with the parent, says what were you told by your doctor, and then they give permission to contact the physician and it all gets squared away. So there is a benefit to the parent of having this extra specialist see the child.

In terms of it increasing the number of birth defects I don't know -- I don't think, Diana, that that is the case. Diana is the one who looks at these things day in and day out that there are not very many situations where the specialist exam picks up a birth defect that

wasn't already noted as some kind of birth defect previously by either maternal report of the medical records. Do you think that is fair to say, Diana?

MS. JOHNSON: Yes. It's happened a few times but it is not something that frequently happens. And our study physician reviews all of the medical records for coding purposes of the major malformations. So that helps as well.

MR. IYASU: Could you comment on the different groups in your study for example, there is exposed group, you have the disease matched, and then you have also the healthy comparison. So if you are looking at recruitment strategies and all the other parameters in terms of retention, your loss to follow-up; can you comment on what the drivers have been for enrollment for the different groups and if there is differences as to retention. I mean you talked about the 5% or less than 5% loss to follow up.

MS. CHAMBERS: Uh-huh.

MR. IYASU: So how do you balance out

all this and --

MS. CHAMBERS: Good question. So clearly there are different drivers for different people. But as I think was mentioned previously by Elise that women may be anxious about the medication that they are taking but I think they do understand that they are not going to help change the outcome of their pregnancy by participating in the pregnancy registry. What they are going to change is the outcome -- or the level of anxiety that women, their sister or their friend, or the next person down the line who becomes pregnant and either has to take this medication or has inadvertently become pregnant what they have to deal with and their clinician has to deal with in trying to understand what is the best thing to do. And that is palpable at the time that they enroll; that that is so important to them that they be able to make that better for the next person who comes along.

And I think that is true in the disease matched group as well because the way that it is

presented to them is we need to learn more not only about drug X, Y, and Z but about the disease that you have in pregnancy. And it is true I think for multiple sclerosis and for many diseases that when you scour the literature not a whole lot is known about the disease itself and disease activity and how that contributes to pregnancy outcome. So I think the level of motivation maybe for a little different reason may be different in the two groups but the exposed and disease matched group pretty similar reasons for participation.

The people in the healthy comparison group are just the golden people of the world because they are willing to do this to help other women because they don't have the condition. They don't have a very complicated pregnancy but they can appreciate the anxiety that people feel and they are likely will have to take a few medications in pregnancy as well and so do it for altruistic reasons.

In terms of how that affect retention I think there is a little bit higher loss to follow

up in the healthy comparison group and that is I think sort of to be expected. But certainly not -- we are never in the 20% range, we can be down in the 8% range for healthy comparison women. And in the exposed and disease matched group once they are enrolled the retention rates are just excellent.

DR. SCOTT: Thank you. So we are going to move on to the next presenter. The next presenter is Dr. Michael Greene. He is going to give an Obstetricians' prospective. And Dr. Greene is professor of Obstetrics, Gynecology and Reproductive Biology at Harvard Medical School. Thank you.

DR. GREENE: Thank you. Thank you very much Dr. Sahin especially for this invitation. My credentials here come from --. So these are my disclosures.

My reason for being here is that I'm an actively practicing obstetrician. I see pregnant women every week. And I'm trying to bring you the perspective from, if you will, the obstetrical

trenches to the Food and Drug Administration.

These are my disclosures.

The next several slides are just a quick run through of the electronic medical record screens that we complete as we see a new patient. First establishing a current pregnancy dating, how did the patient become pregnant? Was it regular pregnancy? Was it an assisted reproductive technology, et cetera?

This is her past obstetrical history if she has one or if she is a primigravida we skip that page.

This is a review of the patient's past medical history which is fairly extensive and when we create an electronic medical record like this we have to balance having a lot of blank pages versus prompting functions. So we try to make the menus that appear for each of these disease classifications or disorders that are specific to not only women but also women of the pregnancy age group.

This is information that is unique to a

prenatal record. Some of the other information that you are going to see is generic for any electronic medical record whether a patient is a male or a female, pregnant or not. But this is more specific for pregnant women; that information that an obstetrician needs to accumulate to provide proper care for the patient.

Family history is generic, history of past procedures, surgeries and other procedures that are germane.

A physical examination needs to be completed. Complete physical exam.

And then finally the care and feeding of a problem list which providers can use to keep track of a patient's problems to make sure that they are addressed appropriately during the course of prenatal care.

The content of the first visit and these slides are borrowed very heavily from the guidelines for perinatal care which is a joint publication produced collaboratively by the American College of Obstetricians and

Gynecologists as well as the American Academy of Pediatrics. The most recent edition is the 7th and was published in 2012. But this specifies the scope of care that is a part of prenatal care for every patient: that at the first visit the doctor should discuss the scope of care or a midwife, whoever the provider is; laboratory studies and their indications; the expected course of the pregnancy; signs and symptoms to be reported; roles of the members of the health care provider team; anticipated schedule of visits; whether the MD. or a certified nurse midwife will be scheduled for labor and delivery and what that coverage entails;, the cost to the patient of prenatal care and delivery which is as we are learning more and more every day is almost an unknowable number; practices to promote health care and health maintenance; psycho-social topics in pregnancy and post-partum period; the content of the psycho-social risks screening; and counseling includes assessing the desire for pregnancy, wantedness for

pregnancy has been well known as an important determinate of ultimate pregnancy outcome; issues with respect to substance use and abuse, tobacco, of course, being the only substance that when used according to direction leads to death, but as well as alcohol, mood altering drugs et cetera; issue of clinical depression; and intimate partner violence. This is from AHRQ. There was a credit to AHRQ on the original slide as submitted. I see it is missing from this slide but anyway but anyway this is from AHRQ about counseling with respect to tobacco.

This is a slide lent to me by my pediatric colleague, Dr. Leslie Kerzner, which is simply a collection of recent front page articles from the Boston Globe about issues with respect to neonatal abstinence syndrome and the increasing frequency of neonatal abstinence syndrome. The Department of Children and Families in Massachusetts has been under tremendous scrutiny recently for some very high profile deaths of children supposedly under protection of DCF but

who were with parents and did not do well or died. Neonatal abstinence syndrome is increasing. This is data through 2009 and this rate has continued to rise. This was a recent article from the Boston Globe again on the incidences of neonatal abstinence syndrome and babies "born with drugs in their system" at one of our local hospitals. This is a community hospital where most people would not expect large numbers of babies to be born with "drugs in their systems". But it is a common problem and all of these issues need to be addressed. This is a very high profile case in Massachusetts which actually was just resolved yesterday with a guilty plea. Intimate partner violence is a serious issue. All of these issues are important. None of them can be dismissed.

In addition to the issues with respect to counseling at the initial visit all of these laboratory studies need to be ordered. And they need to be discussed with the patient after they have returned. Yet more laboratory testing recommended for all or most patients.

Indications for first trimester ultrasound examination need to be reviewed by the provider. And if appropriately indicated to be ordered and obtained.

There is rapidly expanding indications for screening for diabetes. The latest recommendations if taken literally according to some of the agencies that have made these recommendations could lead up to 17 or 18% of all pregnant women being diagnosed with gestational diabetes.

In addition first trimester counseling should include information about nutrition and weight gain, avoidance of food borne infections such as Listeria and Toxin, exercise, dental care, nausea and vomiting of pregnancy, obviously a very common symptom, vitamin and mineral toxicity including mercury and fish intake, avoidance of teratogens, air travel, prenatal diagnosis.

This is from the Food and Drug Administration's own website about issues with respect to mercury in fish including a list of

fish to be avoided that the health care provider should review with the patient.

These are the ethnic background issues that should be kept in mind with respect to screening for a variety of genetic disorders and women who should be screened. The American College some years ago crossed the river and recommended that all pregnant women regardless of age should be offered screening for Down syndrome and that process of screening for Down syndrome is one that has changed very rapidly in recent years. This has been a case of fasten your seatbelts because the technology for screening has advanced way quicker than most obstetricians knowledge and understanding of the technology.

So this was a paper in Nature in 2012 discussing the fact that fetal genes can be detected in maternal blood using cell-free DNA technologies and seemingly overnight no less than four companies appeared in the United States offering this cell-free fetal DNA technology which has been a leap in prenatal diagnosis.

And this is the inevitable slide that I always get out of order but this is Institute of Medicine Guidelines for weight gain which was pertinent to one of the previous slides. And I apologize it is out of order.

And just a couple of months ago the lead article in the New England Journal of Medicine was about the new DNA sequencing versus Standard Prenatal Aneuploidy Screening demonstrating superiority with respect to the number of false positives and false negatives with modern prenatal screening using cell- free fetal DNA in the maternal circulation which is non-invasive and something that encourages many more women to request prenatal diagnosis.

So the point of presenting the preceding slides is to help you appreciate that obstetrical health care providers are under constant pressure to provide an increasingly wider array of health care services within the context of obstetrical care while simultaneously holding the line on or reducing health care expenses.

The consequences of this expanded definition of routine obstetrical care include a rapid expansion of the knowledge base needed to practice obstetrics and hence as Tina was saying their obstetricians are only too eager to enlist the help of any ancillary personnel, genetics counselors and others, people from Teratogen Information Services to assist with counseling for their patients and decreasing time available to address each of the individual elements of care.

In my time as the chair of the committee on OB practice some years ago before my colleague Dr. Ecker, it was a common occurrence for various interest groups who had legitimate concerns about things that we needed to bring to the attention of our patients, about things that we needed to attend to for and on behalf of our patients, to bring these issues to our attention. And each one of them was worthy and important and couldn't be dismissed. And each one only took four or five minutes. But that gobbles up an hour pretty quickly.

Any system I think that depends entirely on obstetrical clinical care providers to identify women taking medications for which there are active registries and pair those patients up with the appropriate registries is likely to result in poor ascertainment and poor patient accrual. Supplementary methods are needed.

So some potential solutions. So by my count so far today I am the fourth person to mention electronic medical records and their potential utility in assisting with registration for registries. This is a screen shot of several medications that when we attempt to prescribe in our electronic medical records system come with some sort of warning that if this patient is pregnant or is potentially pregnant think twice about whether you ought to prescribe the medication. As Dr. Ecker mentioned a few minutes ago the electronic medical record is smart enough to recognize when patients are pregnant, if there is a positive blood pregnancy test in the electronic medical record system and in the

laboratory reporting system it knows that. And these warnings are even stronger than you see here which are generic for any person to whom this medication is potentially being prescribed. These are just some representative warning screens. They are yellow lights. They are not red lights. You can still pass them. But they are warnings that there may be issues with respect to these medications and their use during pregnancy.

This is the FDA's screen shot from the FDA's website list of pregnancy exposure registries and when I counted the number of registries that were listed on the site at the beginning of May when I prepared this slide I counted about 58 registries that were listed. That is not as you have learned today that is not 58 medications because many of those registries include multiple medications. But there are only 58 registries and I would guess that if all the medications were counted up amongst those 58 registries there is probably not more than 200 or 300 would be my guess although I haven't done a

formal count.

This is the first page -- oh there is the number 58, I knew I wrote it someplace. This was the first page of the pregnancy registry list, starting, it is alphabetical order, Abilify is A-B and that leads the list and I just scrolled down real quickly and cut and pasted the Ribavirin Pregnancy Registry for which I serve on the advisory committee. This is the first page that you get when you go to the Ribavirin Pregnancy Registry.

So what potential solutions might there be. Well as already suggested again by others there could be a link in the electronic medical record to notify the provider if a registry is available for a prescribed medication. It is not too much of a leap I think to envision a situation where the electronic medical record links to the FDA's registry for registry sites and provides information to the health care provider immediately at the time of prescription of the medication, often with the patient sitting right

in front of him or her that provides information with respect to a website.

A lot of things can be imagined. The patient could be asked if she would like to be contacted. We could put in the patient's email address. We could give her an 800 number depending upon how the patient would prefer to be contacted; whether she would like to make the initial contact or whether she would be willing to have the registry make the initial contact. I don't think that is too far- fetched and with meaningful use as mentioned earlier again everybody is going to need to be using an electronic medical record. And everybody is going to be doing electronic prescribing.

At our institution paper and pen prescriptions disappeared years ago. And as also many of you are probably familiar the system for encouraging meaningful use will rapidly transfer from a carrot to a stick. So previously you were getting a bonus if you were using it. In the future you will be penalized if you don't use it.

And then finally as I mentioned earlier and Alan pioneered this I think with the Accutane Registry is that through prescription benefits providers will notify patients directly when they fill prescriptions. The large prescription benefit providers will be able to notify patients directly when they fill a prescription for a medication for which there is a registry.

So those are a few of my thoughts. Thank you for your attention.

[Applause.]

DR. SCOTT: Okay. We are going to move on. And we will have clarifying questions for you in a little while.

So the next presenter is going to be Julia Beck who is going to give a patient perspective on pregnancy exposure registries.

MS. BECK: Hi there. My name is Julia Beck. And as noted I am a person who spends my days at a company called Forty Weeks that I founded specifically to help brands find ways to develop creative strategies to connect with known

expectant parents. So I spend my days engaging expectant women. So you guys go lucky today, you got a twofer.

But the story actually is a more important one and that is one of being a patient. And that is one of being a woman who had secondary epilepsy as the result of a near death bout with viral encephalitis, found herself in her mid 20's. I really wanted to have children and it was scary. It was a very scary time. There was not a lot of information. This was the '90s, the late '90s. Dr. Holmes I think I was one of the first people on your registry in '98 I first got on that registry. But it was scary and I was very much in need of information. There was not a lot to be had.

And so I basically vowed that once I figured out how this was going to happen, how information was going to be collected and shared and how communities would be built to support women like me who needed a solution I would support all the way through. I have been.

I have been participating as a media voice and as counsel as best I can.

But to go back to how I ended up on a registry in the first place; it was because I was digging around and there was nothing there. And I think that is a really important bit of information. This was sort of early. Again think of now as sort of registry 2.0. This was way back when when there was hardly information to be found. And I dug and I dug until I did find out about the registry at Mass. General.

I wasn't told by an OB and I wasn't certainly told by my neurologist. But I participated. So the first one I registered for in January when I was pregnant with my daughter who is turning 16, the first one was January 1998 and I participated in that.

I later participated in a second one with my son who is turning 12 so that was 2002. I think the important bit was that it really felt important to try to find a way to connect with other people who had the same situation, the same

challenges. I think the hardest part was there wasn't a lot of data yet to be given back. So it felt a little less fulfilling that I had hoped in the sense that there was not much for me to learn from it. I don't think I got my first report until -- or information shared I guess until I was already pregnant with my second child.

But it appears to be really getting pithier. It doesn't seem that there is the same dearth of information. It seems that there is more out there.

I have tried to with moderate success to share the importance of this registry. I have to be honest; I didn't know about the others. So you got all my benefit. But I have done my best to share this information with the clients that I work with because really my specialty is bringing my private sector clients, my for-profit clients to make social responsibility and public health agendas part of their marketing initiatives.

And, of course, this is not quite as widely embraced as challenges such as work that I

am doing at Ronald McDonald House or work that I am doing with regard to issues of back to work and breast feeding but still I share it with all the magazines that I can connect with. I do what I can.

I think though what might be interesting to think about is and again, I am moving a little bit away from my patient hat, a little bit over to my professional hat, thinking a bit about where these silos are of concentration. There is not a huge concentration of young women with epilepsy who are trying to conceive. You see more of a concentration with anxiety and mood and depression for example where there is more of a community that is already openly sharing and openly engaged with a conversation about concerns about staying on or off meds during pregnancy and what that might net.

With epilepsy I had no choice. It was a secondary epilepsy. I had just recovered from an illness. I certainly wasn't going to take a chance of getting off of a med.

One comment though about these registries. You are all talking about something that was very very important which was would there be a malformation of my child. These children are now older. They are teenagers and there are things that they have that who knows where the correlation was. And maybe that is not relevant to this conversation. But I have one kid who had a sensory integration disorder. I don't know. But maybe it is a conversation worth extending if you are able to engage these women for longer, follow them for longer.

I am not anywhere near as qualified as any of you but I do know that there is a question that happens. It is a long season raising children and you just -- I don't know. I don't know. But they both turned out quite healthy to start. So how is that?

I think the opportunity though to engage and to share is really your opportunity. I think it was Kate Ryan who spoke about the opportunity for engagement and I couldn't agree with that

more. I think that you are reaching people at a place where they are desirous of information, they are desirous of community and they are looking for a way to feel connected with other individuals. And that is engagement. And with that engagement comes an understanding. There is almost a quid pro quo they will be more willing to share with you for longer period of time if you will do the same with them.

As somebody who has been on a registry and I will be forever be in support of these I guess that is my biggest take away.

[Applause.]

DR. SCOTT: We have some time for some clarifying questions from the panel to the presenters. And let's start with questions from the panel for Dr. Greene and then Julia and then it can just be general. Okay.

Any questions --

MS. ANDRADE: Hi. This is Susan Andrade. Dr. Greene I just had one comment. I know you mentioned having an alert to identify

women who might be eligible for pregnancy registry and I know there is always a lot of concern that there's alert overload in a lot of these systems. And I am not sure if this is a question for you or the group. Is there some way that these alerts can kind of rise to the top so that people just won't skip over them because they have already seen like the fifth alert for this one patient within two minutes?

DR. GREENE: Yes. Mike Greene. That is an important issue. You are absolutely correct. There is alert overload and electronic medical records make it easy and foster alert overloads.

The flip side of that, however, of course, is that you know how many medications are in the PDR and there are what 1200, 1600 medications in the Physician's Desk Reference. And there are only maybe 200, maybe 300 for which there are pregnancy registries so that the majority of medications that a physician or midwife, whoever, is going to prescribe in the

normal course of events for which one of these alerts will come up is going to be hopefully pretty small.

And the other issue that I will mention, the flip side is that many of the alerts are inappropriate. They are false positives. And that fosters ignoring alerts. Okay. Hopefully if people realize that the match is good that when it says Valproate and Valproate in the registry it is the same thing and that is a real concern, not just a close or near miss that should be dismissed. So yeah there has got to be a good both sensitivity and specificity of the alerting system.

DR. SCOTT: Any other questions for Dr. Greene? Any questions for Julia Beck from the panel?

Okay. So I will just open it up for general questions to any of the presenters from the panel?

Are there any questions from the phone?

MS. TASSINARI: I am not sure where this

question lies in all of this but we've talked a lot about electronic health records. And I have the sense that there are electronic health records that are in UC San Diego and there are some in Mass. General and there are some in all sorts of different places. Is there a standard? Where is the complication in us, meaning FDA, thinking about encouraging a best practice for example of using electronic health records and running into a situation where there is the inability to cross talk or the inability to expect that we are getting the same standards across all of this. I am not invested enough in the EHR to know where we are in standardization and harmonization. I wonder if you could comment.

DR. GEENE: This is Mike Greene. I don't pretend to be an expert on the overall electronic medical recordization of the United States. However, there are a relatively small number of commercial providers of electronic health records that are coming to the surface that will control the vast majority of the electronic

medical record market. The degree to which they are compatible is to paraphrase another public official what do you mean by compatible. So most of the electronic medical records will -- their output will be as basically pdf files. So human beings can read them. Okay. But they are not necessarily defined fields that will transfer over from one record to the next; so that a human being reading the record will understand the record from one university or one medical center to another.

Now the other advance that is already here and getting better every day is what is called natural language processing; so that computers will very soon be able to read English and understand it as well as or better than you and me. And they will understand that what one health care provider calls this and another health care provider calls that are actually the same thing. So that is advancing.

But in terms of a controlled vocabulary and defined fields in electronic medical records no I don't think that there is going to be a

compatibility standard at least initially so that an electronic medical record at UC San Diego can be imported into our electronic medical record in Boston and all the data is going to find itself to the right places.

I don't think that is going to happen any time soon. But it will be readable by human beings.

DR. CHAMBERS: I can add to that a little bit because we are expanding the preconception one to UCLA. And so the program we are trying to write the smartset for that is negligible that they think they can just take what has been done and they have a different system. What has been done at our institution and write it to fit theirs. So and I agree with Michael that there is not an infinite number of types of software that are used for this that potentially could be done so that it applied to all of them.

DR. GREENE: Just one skeptical note is that until it's done it isn't done. Okay. And they think it is negligible but until it's done we

have a lot of experience with programmers who say oh this is going to be easy and two years later they are still working on it. So --

MS. COSTER: Trinka Coster. On the part about -- I guess I have a concern with the health records being transferred to so many registries and then kept indefinitely. And I would suspect a lot of patients have problems with that just because there is constantly so much loss of identity.

And with new technology I mean why not leave the records behind the firewalls where they belong and use other methods to verify your diagnosis such as like you are saying you could put in that they had to have this exam, this exam, this exam and essentially use the technologies since everything is electronic anyway to gather your data that way and then you are only passing aggregated information rather than down to the specific of birth date, social security numbers, all that kind of stuff. And I was just wondering if as you move forward if you would look at

technology that would leave the medical records behind the firewalls and just take aggregated information so that you are maintaining the privacy of the patients.

And I think if you considered that you'd probably have a lot more participation because I think people are concerned not only for themselves but possibly for their children to have their records indefinitely held could upset a lot of mothers. But that is just what I am thinking.

MS. CHAMBERS: I think that addresses the issue that we are not -- we don't really understand what the barriers are. So is the concern that it is something will happen five years from now. Is the concern that there is going to be something in the record that states something about genetic disease or something that wasn't part of what they agreed to release and so on. So I think a better understanding of what are the barriers to doing that.

From the standpoint of getting aggregate data what we do with medical records at least the

way we do it is we are abstracting very specific information from those records, not just the diagnosis of the birth defect but prenatal tests and so on that ultimately go into the individual analysis of potential confounding and exposure and outcome for that patient. So being able to link it to a specific patient is important which is not to say that ultimately to the extent that it could be de- identified, the record could be de-identified once that linkage is made. So if that is what you are thinking of yes I think that is possible.

DR. GREENE: Mike Greene: One comment I'd just like to make with respect to de-identifying records is that Dr. Octo Barnett was one of the pioneers of electronic medical records starting almost 40 years ago. And he taught me quite a bit. And one of the things that he always said was that with five or six key pieces of demographic information you can identify pretty much anybody. Okay. So if you know that the sex of the mother is female, you know her date of

birth because you need that as an essential piece of information, you know the date of birth of the child, you know the sex of the child and you know what the birth defect; it is very easy to identify people even with de-identified data.

MS. COSTER: I agree with that but you have to then ask do you need the exact -- can you start looking at ranges or putting in algorithms that switch that. And I think we certainly have looked at that where you just basically put in an algorithm that changes all the dates by one year but it keeps all the relationships of every visit. So you can do things that better anonymize. And then you have to ask does it matter if I am 50 or 51 so you start thinking about age ranges so that you are not exactly -- so I think there are things we can do that actually benefit the patients rather than having kind of the way we've always thought just having a birth date.

DR. SCOTT: I have a question for Dr. Chambers. In one of the morning's presentations we saw data that showed that the women who

participate in pregnancy registries are generally well educated. And so I was curious what impact, if any, did you think that the increased use of these electronic data collection methods such as the personal web portal that you mentioned will have on the "representativeness" of the people participating in the registries?

MS. CHAMBERS: So I think that the primary goal of those kinds of approaches would be to increase completion of data collection but a secondary goal certainly could be to increase diversity. So whatever the barriers are to diversity and that is as I think Lew Holmes is the one that presented some data about who participates in a registry tends to be higher social economic status more prevalently, not women of color, and that is true for us as well. It does vary by exposure. So we get more diversity for some patients than others but I think that exploring ways and that might be one of them that might improve diversity is a goal of ours to be able to do that. Because clearly not that the

necessary result of the fact that these tend to be higher social economic status better educated women leads to false conclusions from what the comparisons are that we are making but that we would like to be able to make this as generalizable as possible as well as increase the sample size by drawing on a broader group of people who might be eligible to enroll.

MS. TASSINARI: If we have time for one last question I have one for Ms. Beck. Reflecting on your commentary about your experiences trying to find information and getting yourself enrolled in the registry. And now in your conversations with people telling them about your experiences are they having the same difficulty finding out about registries or have you found that it is a little easier for them to get that support that they need?

MS. BECK: Well first of all there has been such a just a growth of information targeting new and expectant women; right. And so the idea of targeting new and expectant parents is

completely in a new place than it was -- remember we are talking about 1998. That is a long time ago.

The information connection is a much different currency than it was then and so women are willing to work harder to find those communities and again willing to be more loyal. Are they still having an issue finding this particular, the IDF registry? Yes. Yes, because it is not aligned with other parts of the way that pregnant women are being communicated to. So there is an excitement to it. There is an exuberance to it. There is a lot of stuff that is sort of an easy way in as opposed to the rougher way in. So there are a lot of opportunities to connect. I talk about this all the time. Start with baby names and nursery decor and you are golden; right. Because there is no way to really fall down there; there is no sad scary outcome there. And so that is what I would tell for example somebody trying to talk about nursing, don't start with something hard, start with

something easy.

But the same thing might apply to talking about registry. Just on a checklist of what it is you need to be thinking about as an expectant woman; something as simple as that would open a dialogue.

Does that answer the question? Yes.

DR. SCOTT: We have time for one more question before the break.

Okay.

MS. MOYER: We are just on exact schedule which is fantastic. We are going to break for 15 minutes and we will resume at 3:35.

At that time we will start our panel discussion and question and answer.

Thank you.

(WHEREUPON, a break was taken.)

MS. MOYER: If the panelists can please take your seats.

DR. SCOTT: Welcome back. Can everyone please take their seats? We are getting ready to get started.

So we are going to start the Topic 2 panel discussion. And we are going to focus in on three questions related to enrollment, retention and communication. But this time period is also a time period in which the panel members can also ask questions or comment on any of the materials that were presented this afternoon including presentations made during the public comment period.

So let's get started with our first question which is: How can enrollment retention and pregnancy registries be improved? And in answering or discussing this question we want you to consider how do we overcome barriers to enrollment; the use of enrollment and study participant incentives; and then also how do we minimize the loss to follow up.

So I would like to open up the panel discussion with this question.

DR. HOLMES: Lewis Holmes from the North American AED Pregnancy Registry. A comment on informed consent as it related to enrollment. We

had the same problem when we mailed a consent form to women, they had great difficulty signing that and sending it back which seems hard to believe. But they did. So the good news was the IRB allowed us to do a verbal consent. And I think for pregnancy registries if you are setting one up it is really the way to go because even though it might seem logical that the easy, the women are still pregnant, they are not involved in taking care of a child, they ought to be able to receive a consent form, sign it, send it back, it just doesn't work. So that is an issue to help with enrollment.

MS. BERLINER: I just want to comment on Tina's presentation that the system that you described it has a lot of synergy with stuff we talk about at AHRQ which is really building a patient centered research infrastructure. So a lot of the things that Tina talked about about like being a center of information for patients; really considering the patients to be partners in the research. I think those are all things that I

think are really helpful and it shows in having only a five percent loss to follow up.

DR. SCOTT: Dr. Greene.

DR. GREENE: Mike Greene. Lew can I just ask you how many pages long was your consent form that you sent to the patients?

[Laughter.]

MR. HOLMES: Since you work at the same institution you know it is going to be eight, nine, ten pages long with all these mandatory paragraphs that would scare anybody to death.

[Laughter.]

MR. HOLMES: But we were running about a 50% sign and return rate and -- your point is well taken, yes.

DR. SCOTT: Yes.

MR. MITCHELL: A couple of comments. I am not sure a shorter consent would do any better because then it would actually get read.

[Laughter.]

MR. MITCHELL: And there is one subset of people that do read the entire --

DR. GREENE: They are called lawyers.

MR. MITCHELL: Yes.

[Laughter.]

MR. MITCHELL: A couple of things. First I got an email from Peg Honein so I am going to channel Peg Honein because her cell phone or whatever phone she was using was not very clear. And the NBDPS study that CDC has orchestrated did do -- we're involved with that as well, did do a test of an incentive, a financial incentive for participation in the study. And I can't remember the dollar amounts, I can get them. But it turned out that there was a disproportionate benefit on enrollment for minority, lower SES. So there is some evidence to suggest that a financial incentive could actually not only benefit some aspect of enrollment but could target the populations that are typically underserved.

And then to switch gears in the presentation about some focus groups for Office of Women's Health which was really fascinating. One of the things that struck me was one of the women

said something about the word registry having a negative connotation and it really made me wonder. And I just throw it open to others on the panel. When I think of registry independent of a pregnancy registry I think of Registry of Motor Vehicles, I think of people mentioned cancer registries, you think of NSA; need I say more? So I wonder if the word registry itself is a turnoff. And has anyone explored that. I can't answer the question.

MS. THOMAS: I know what we found in the usability testing was not so much that it was negative that people just would not click on it. What resonated was medicine and pregnancy and having those words caught people's attention and that is what they were interested in. But when they saw the word pregnancy registry, it wasn't so much that they were turned off, it was just that if you are faced with a lot of different ads, a lot of different pop-ups on your computer screen that might not be one that would catch their attention. But I think if you package registry

with terminology that would be of interest to women then they would be interested. They would click on it.

MR. MITCHELL: Well I am just thinking in the shorthand and I'd really like to hear what you have to say as well but in the shorthand that a physician or health care provider necessarily has to use if they are going to encourage women to participate they are not going to -- I don't think they are going to have the time to go into some of these subtle distinctions. And the word group or something that suggests that you are one of a group of like people who can make a contribution and benefit because I agree with you. I agree with the other comments in our own studies as well altruism is the main driver. It is remarkable how altruistic people are when presented the opportunity. But again I just wonder if some marketing person came up with a different label. And Julia --

MS. BECK: So the word registry actually in pregnancy has to do with that wonderful gift

registry that you sign up for at Babies R Us and it has a whole different connotation than what you are intending. And I think what Kimberly is saying is right. They are clicking -- it is a disconnect. And I think you are right a re-labeling or a repositioning to put it in the category of this is a community that I belong to, there is information here for me, and there is a way for me to help. I mean you could connect it to Babies R Us Registry, there is a lot of population there, there is no question about that. But I think it is a disconnect name wise.

DR. SCOTT: I have a general question to the panel. We talked about incentives in terms of financial incentives. What other kinds of incentives do you think would be helpful in terms of retaining participants in pregnancy exposure registries?

MS. BECK: So it almost circles right back to what we were just talking about with regard to gear. All populations regardless of economics it is a whole new universe of things you

need to purchase at a point of pregnancy. And what would be interesting about partnering with somebody to give gear instead of cash is then you would benefit from their advertising, their marketing, their PR.

They could proudly say they are supporting the growth of this registry by giving a diaper bag; I am making this up, a diaper bag as an incentive for being a part of it. So not only did you get the exposure to an incentive but you also got the exposure to somebody else's marketing amplification potential.

DR. SCOTT: Dr. Hernandez-Diaz?

DR. HERNANDEZ-DIAZ: I think I also hear from the participants that if perhaps we were to give women back more information, more access to the findings that that might make them feel more a part of the registry rather than just only giving and not getting anything in return.

DR. SCOTT: Okay.

MS. BERLINER: Yeah. I think even like having a newsletter that says here are the

findings, you helped make this possible.

DR. SCOTT: Dr. Holmes?

DR. HOLMES: Two things. We've used a raffle as a way of rewarding people. So if a woman refers a friend or a family member as a comparison group participant she's -- her name is entered into a raffle as well as the comparison person. And it is like $400 I think they are gift cards. And the odds of her actually winning this are probably in the one percent range. It is like after 100 women enroll then we have the raffle and somebody gets that $400 gift certificate.

The other issue is the newsletter. We've been sending out a newsletter once a year for quite some time and we see in the enrollment it always ticks up significantly for both the unexposed and the exposed. So and it has turned out to be an effective way of keeping people aware the registry exists because a lot of people if it is too long an interval they will say we wondered if you were still operational. So is that

helpful.

DR. SCOTT: Thank you.

MS. YAO: I don't want to shift topics completely but I think I have heard a lot this afternoon about again the need to engage a pregnant woman directly. I haven't completely given up the notion; I hope not, that there is a way to engage the health care providers a little bit more to participate in this endeavor.

So this one concept has been percolating in my mind for a while and I would love to hear the panel's opinion on tying in some way now that we have all these requirements to maintain board certification with our own specialties this concept of maintenance of certification or MOC that I know many of us are dealing with to maintain certification. And I do wonder do you think there is a way to tie in the need to collect these data to encourage professionals to enroll them in registries with a maintenance of certification because it seems like a way to incentivize or encourage people to participate in

the public health of their specialties. And use that to allow them to maintain certification. So I am throwing it out there because I would love to hear what the panel thinks and whether or not we should be engaging the various professional boards.

MS. CHAMBERS: I don't get certification so I can't comment from a physician's standpoint but I do think that it is wrong to ignore the providers. And when it comes to the provider playing a role that I think our experience has been that if a pregnant woman is encouraged by her provider to enroll that is a huge leap up; that they will do it because the provider says this is a good thing to do. So it is incredibly important for the provider to think that it is a good thing to do. And part of that is getting -- giving something back to the provider.

So whether it is the incentive of a certification perk or it is that they get feedback on what happened with their patient or they get feedback on what is happening with the whole

study. And maybe it goes back to the newsletter thing that it is really important to make the provider feel as valued as possible for the really important impact they can have on getting a woman to enroll.

DR. SCOTT: Are there any other suggestions for incentives for health care providers?

Dr. Hernandez-Diaz?

DR. HERNANDEZ-DIAZ: On the same point some information that may help the discussion I was asked this morning about the proportion of women from the North American Anti-Epileptic Pregnancy Registry that report us to enroll because their provider referred them versus the website versus other sources like the label. And Kathleen Smith the study coordinator sent me the data and overall over the years around 85% of women enrolled because they enrolled or their prescribers refer them to the registry. Not that they enroll the women but let the women know about it and so I think the providers are key and I

agree that they have to be part of it. And I don't know if the grates would work but certainly I think after they receive the information and then enroll in epilepsy meetings, they get to the information that the registry has and I think they appreciate being able to see the updated information on the newsletter. So yes, I definitely think they are an important part of it.

And just one more comment that perhaps the enrollment has two parts of it: one is women being aware of the existence of the registry and then a second step, they enroll. And perhaps the website have more of a role in that enrollment part once somebody tells them about the registry, they go to the website and then depending on how appealing it is, that might influence the likelihood to enroll and click.

MS. BERLINER: I am wondering which provider really has ownership because it is like if you have a woman with a co-morbid medical condition and it is like the obstetrician is in charge of the pregnancy and the other physician is

in charge of the woman's medical condition so who is really in charge of the interaction. And again one of the things that Tina said that just really resonated with me is the idea of having someone to consult with; right. So if you are an obstetrician with a patient with epilepsy and you only have a handful of patients with epilepsy it is not really your expertise but who can you -- who can help that patient and if you're a doctor treating epilepsy how many of your patients are pregnant. So it is really having a place to go to send the patient to get more information on the interaction.

MS. THOMAS: I'd like to add something. One of the things that we've seen is that the free continuing education courses are a good tool to raise awareness among a variety of different types of health care providers. And they are very receptive to being able to: one, get credits that can help them with whatever certifications or things that they need but also they are getting the information. So that it may not necessarily

be tied to them signing up someone for a registry at that moment but you're are bringing it to the forefront of their mind. You're talking about the resources, you're talking about the information that we have available so that it is there for them and they may be more likely to refer someone later on. So I think a continuing -- a free continuing education course for not just for physician but for nurses and pharmacists would be a very helpful way to raise awareness among health care providers.

MR. MITCHELL: Yeah. I guess one thing that I wouldn't want to get lost in the shuffle here is -- has already been touched on but I think it is generally accepted that patients find their physicians the most trusted source for medical information. And the alternative is a patient God forbid going on Google. Julia you said you didn't have any resources. Now we've got too many.

MS. BECK: That is true.

MR. MITCHELL: And the ability to sort the real from the imagined is beyond the canon of

most lay people, most professionals.

So I think one of the things that a provider can do in the context that Tina described is by directing their patient to a Teratogen Information Service or Mother to Baby to answer questions that not only provides them a vetted source of information and avoids misinformation but it also opens the door to participation and research. So in a sense the provider can kill two birds with one stone. They can refer the patient to a trusted source for information about medications they might be taking and at the same time it could enhance enrollment because there are that many more people calling. And they are calling because their provider suggested it.

MS. ALBANO: One of the things, this is Jessica Albano, that the APR does when they publish their semi-annual interim reports is to recognize some of the physicians who have reported cases. And we have some minimum criteria of cases that need to be reported, specific quality et cetera. But as a way that that can take some

ownership that they have contributed to the data that is being reported.

DR. SCOTT: Do you have any comments for those on the phone?

Okay. We are going to move on to the -- I am sorry. Yes.

MS. DANA: It is Adrian Dana. I just wanted to say that in our registries you know we work really hand in hand with the providers and we do as a requirement of enrollment we do need to have a provider involved and one of the things that we do do and one of the reasons that we actually do prepare periodic, usually annual reports is that when a provider calls they are actually most of the time looking for information more than enrolling into the registry. And so at that point we have a contact where we are able to ask them to enroll the patient that has been exposed that they have. And then we are able to provide for them the most recent annual report which gives them whatever information we as a company have, good information. It forms a basis

for counseling and informing their patient. And so we do feel that we work hand in hand and we take this obligation to provide that information to the providers very seriously so that they can use that information. And so I do think that is one real advantage for the preparation of routine periodic reports so that we can provide that to people for counseling purposes.

DR. SCOTT: Thank you.

Leyla?

DR. SAHIN: I have a question for Diana. So can you talk a little bit about when patients call the Teratogens Information Service and then they get their genetic counseling regarding their exposure to a medication; and then what is the process to get them into a study and what are their perceived barriers? How open are they to the idea? You know they have come here for some information but then all of a sudden they are talked to about recruitment into a study. So could you provide some comments please?

MS. J0HNSON: Sure. So typically the

counseling takes place and the counselor will let the woman know that they may qualify to participate in a research study and would the woman be willing and interested in hearing more about the participation. And if she says yes, she is asked if she would like to be transferred or if she would like a call back. And then our interviewers will give a call back if that is the case or transfer over to an interviewer and discuss come basic elements of participation. Go through just a brief screening. And if she is agreeable then we go through a screening consent to find out if she qualifies and go through a list of questions in terms of whether or not she is willing to take part. And if she is, then we will go through the informed consent.

So most of the time as Tina mentioned women who decline participation either say that they don't feel that they have the time to participate or they are reluctant to release medical records after their pregnancy has completed.

DR. IYASU: Actually I just wanted to ask a question. Maybe Dr. Sahin if you are familiar with the strategies that have been employed by the National Children's Study. I know that there has been some evaluation of different strategies for recruiting pregnant women into the study. And if I recall they were sort of evaluating the tradeoffs between direct patient or pregnant women outreach versus a facility or provider based and I think ultimately they found that the best strategy is really a hybrid. But I don't know if you are familiar with what they decided.

DR. SAHIN: This is for the National Children's Study? It has been a while since I have been involved in anything related to that. Tina do you know?

MS. CHAMBERS: I think the current status is yes a hybrid of provider based recruitment versus direct patient recruitment. And at least as the publications are starting to come out now if it's direct patient recruitment

one of the original strategies was going household to household, the biggest barrier to recruitment was the first person being a male that you contacted.

[Laughter.]

MS. CHAMBERS: Instead of a female.

DR. SCOTT: So we are going to move on to the next question. Question 2 is: How can overall awareness of pregnancy registries as well as the existence of available registries be increased for patients and health care providers? I want to open that up to the panel.

MS. BERLINER: So I heard some criticism before of patients looking at Google but I think that is where patients are going to go and so I just did a little quick search of epilepsy and pregnancy to see what came up. And the first three sites were the Mayo Clinic, the Epilepsy Foundation and WebMD. And they have these nice little sites saying are you thinking of getting pregnant? Here are some things to think about and some information about medication. But not really

very detailed. But is that something that the FDA could make partnerships with those sites so that there could be a link on those sites that say need more information on medication and pregnancy and epilepsy or whatever the condition is then go to the FDA website. Then have more detailed information from the FDA on what is known and not known about the risks of different medications and then an invitation to look at the registries.

So it is just like you know patients are going to be seeking information so how can we leverage that to get them to consider the registries.

MS. THOMAS: Well I think what we've -- this is Kimberly Thomas. I think what we've done is a hybrid of that in the past. We've done some paid Google ads, some in places where our target population is going. So if they are looking at certain videos that have nothing to do with FDA or medicine on YouTube but it is baby related or pregnancy related then we have done ads to have our things pop up there. They watch the video and

it directs them to our website. We've also done ads, just the headline ads to direct people back to the website. And we've done outreach to some of our stakeholders to get them to add links on their website to where we are going. So I think we've done it but it is something we can do more of really going to where people are and making sure we are putting accurate information or links to accurate information even in some of those chat rooms where we know people are talking about things that are incorrect; directing people to the correct information and to the website.

DR. SCOTT: So my question is to Julia. Do you have any suggestions for us in terms of increasing awareness about pregnancy registries among patients?

MS. BECK: I'm thinking about what Kimberly just said and I think there is a difference between availing yourself and establishing yourself as the ultimate resource. And I think that that is again, I am hearing a lot of amazing things today, but then sometimes these

disconnects come up and so this is really the hub of all of this data yet somehow it isn't owned.

And so I am thinking a bit about I think the idea of partnering not just saying we're here but partnering with the assumed places to go for information saying glad you are here because we are the resource, we are the definitive source and we are partnered with them. So the idea that you really put on this hat and say this is the right place. Maybe that is the wrong metaphor, maybe it is more like Lucy's sign but the idea that it is sort of like if you can't beat Google you are going to join Google. You are going to think about how to use it most effectively for you. And whether you like it or not thinking about pregnancy is private or between, if it is planned, it is a very Googled act, it is what it is. So I think there has got to be a way to really then put yourself in the middle of the conversation as opposed to seeing if they show up. Does that answer the question?

DR. SCOTT: Uh-huh.

Do we have any comments from those on the phone?

What about --

DR. CONLON: This is Dr. Conlon at the Naval Health Research Center in San Diego. Again our experience is a little unique I think. But what we've seen as far as referrals from providers working with our vaccine registries is their electronic medical record is now designed to ask about the recommended vaccines in pregnancy to include influenza and Tdap and that seems to alert them to check about those vaccines. But there is nothing in the electronic health record asking if a woman has been exposed to say smallpox vaccine or anthrax vaccine. So maybe those triggers could be helpful.

In our setting too we have the allergy and immunology vaccination clinic that are another somewhat ancillary provider that are good to reach out to because they are seeing these patients, providing the vaccine, and then often when a woman finds out she is pregnant they go back to that

vaccination clinic for the various forms to be followed. So for them to have awareness is helpful.

And I would think that could translate in the medication world to working more closely with pharmacists who are ultimately dispensing the medication to insure that women at that point of care are aware that there might be a registry for the medication that they are picking up at that time.

DR. TASSINARI: So I guess I want to swing back to Lynne's question from earlier because it strikes me as I am listening to this and some of the suggestions which I think are really requiring us to think about using current media to do the job that we want to do for patients. But what do we do about the health care providers?

I am beginning to think there are two streams we have got to get moving here. And what would be your recommendations if we are focused on health care providers here to increase awareness?

DR. HOLMES: This is Lewis Holmes with

North American AED Pregnancy Registry. Melissa we don't have the answer to that but we know from our many years of doing this that this group of cheerleaders has really made the difference. And so I would rephrase your question to say how do you find at a medical meeting or whatever when you are giving the information to 100 people, 500 people, 1,000, how do you identify that subset who is turned on by that information and says hey, I want to help because that is what really matters.

The women will tell me that my doctor's enthusiasm for me calling this toll free number was a key factor in my deciding to do that. And I don't know the answer to this. But getting to those people, not everybody, but that subset who really is interested is what we are talking about. And that made all the difference for us; I am sure other registries as well.

DR. TASSINARI: So I would take that to say it is not that we should be looking at health care providers in general but we should be focusing in on those folks, cheerleaders as you

were calling them, to really help us make sure this awareness grows and do it that way?

DR. HOLMES: I just don't know why if you present something to 100 people only two or three or whatever the number is really say hey, I want to help with that. But that seems to be the way it works. And that is the reality. And, of course, we've targeted some of our follow up marketing to those people. You know just look through the system and say okay who has referred more than three patients or four or whatever the number is and then send information just to them as a way of trying to increase whatever it was we were trying to increase.

DR. SCOTT: Dr. Chambers?

DR. CHAMBERS: I was going to add to what Lew said. I think that by going along with that in any kind of specialty physician group there probably is one or two people who consider themselves the experts on pregnancy for that specialty. And so to have them not on your side is a big negative. So it is important I think to

identify who are the opinion leaders in that particular specialty regarding pregnancy and make sure they understand what the pregnancy registries are about and how it can benefit them.

And the other thing I wanted to say going back to Julia's comment is who owns this and kind of the disconnect. I think neurologists are so familiar with anti-epileptic medications that it spans teratogenicity that it is something that has been on their radar screen for a long time. But you take other specialty physicians and they may not be thinking that very many of the medications that they use have safety issues or potentially could. And when they find out that a patient is pregnant do they pass the responsibility on to the obstetrician and is there a disconnect between the two in terms of who is responsible for making the patient aware of a pregnancy registry existing. And I guess I would say both, that the two need to be talking with each other but the reason the specialty physician really needs to be involved is they are going to

know about it probably earlier than anyone and that is the time when you want the person referred is as early as possible in pregnancy.

DR. HOLMES: This is Lewis Holmes again. That raises the question about trying to use medical meetings of whatever this group is as a way to do that. We benefit from the fact that there is an American Epilepsy Society which is the neurologists with an interest in epilepsy and all aspects. And that organization has set up special interest group meetings at the beginning of the annual meeting and we've been invited along with the other pregnancy registries interested in this group of drugs to come every year and give a ten minute, 12 minute summary of what their latest information is. So that has worked for us in the neurology community. And Mike could speak to or anybody else to other organizations you know what is the likelihood that an OB organization would have a similar interest in having a focus on specific things because that seems to be every year the room is full. It is a room sometimes as

big as this room and it is full and it is mainly people that are going home wanting to know what is the latest on Keppra or whatever because it is a constant question they are asked; and would there be an equivalent in OB and would there be other specialties because that system has seemed to be a great asset.

DR. IYASU: Yes it's Solomon. There have been several comments about information getting back to the provider from the registry and also information gets back to the participants. And I am wondering with respect to the patients what kind of information is a motivator because you wouldn't be able to get information that is pertinent to the drug that they are exposed to within the lifetime of the pregnancy duration and it is long after that you will find some information that is generalizable in a way to women who might be interested in contributing towards knowledge.

So how much of that is a disincentive when you tell them that information may not be

immediately available that would help other women but it is three, five, six years down the road. So in the meantime what do we do in terms of providing information that pregnant women are interested in; what kind of things are we doing to sort of keep them in the registry and actually so that there is follow-up, adequate follow- up. So I am trying to understand what are the kinds of thing that would work actually given that it takes a long time to get that sort of motivator which is what we call altruistic nature of human being to contribute towards knowledge.

DR. COSTER: Or of disseminating information. The Med Page, Medline, FDA alerts that come automatically to physician's email box is a way - - I don't know if the summary on the patient registries hook in with those organizations but you would get a lot of that going right to the email boxes of physicians. And usually what happens with those in large hospital organizations, those are repackaged and sent. And they are also discussed. Now we have the patient

centered medical homes where you talked about a champion usually all you need is one physician in that medical home huddle that is bringing in to their other five or six physicians that work in that clinic that information. So we found it is a pretty effective way of getting that kind of information out -- physicians is like for the FDA alerts that goes right to your email box, the Medline, Med Page when there is announcements, they repackage that and put it out and it goes to people's email box you know hooking in with those already, rather than having to specifically order yours but having it announced so that it actually goes out at a professional meeting. So it is communicated in these kinds of services that most clinicians kind of hook into could be an effective way of getting that information out to your clinicians and as you said you only need maybe one in those patient centered medical homes that then transfer that information.

DR. SCOTT: Do we have any -- I'm sorry.

MS. JOHNSON: I was just going to say

and maybe you can speak to this a bit yourself but in our case I think that most of our subjects understand that it takes a while to gather the information and they understand the period of time that we are going to be taking to gather the information and because they've gone through the counseling and they realize that there isn't much out there, that is why they want to contribute even though they are not going to have the information back in a month or six months or one year. So I think when you go through the process of explaining what is out there and how the information is gathered and how long you are going to take to gather that information. I think most patients understand that and they want to be able to help contribute in the future.

MS. BECK: Well I actually hear that everybody is describing the same basic motivator both physician and patient. It is somebody who has the ability to really latch on to the problem and a desire to be altruistic as you said and part of the solution. And I wonder again, I understand

there is HIPAA and there are other things but what about some sort of content that could live on the website for example that called out people who have been exemplary; physicians who have done an amazing job of sending patients to a registry and highlighting patients, maybe coupled even with that doctor showing the journey that they've gone on together. And really somehow just giving credit where credit is due in a way that might inspire others. I mean this is from the physician's side but it is a just a working thought.

DR. MITCHELL: Alan Mitchell. One of the things that may be helpful because it is of course the case that the women who enroll in the registry are not going to benefit directly from the results of that unless they become pregnant again but providing intermittent progress reports in a global sense is a sort of self-reinforcing process where the women now see themselves as part of a larger whole and may be more motivated. I think in a registry that is 95% retention it is

not, there is not much margin to improve. But in general I think the fact that women know that there are X hundred other people, perhaps they are in these stages of follow up and the participation rates are such and so, that kind of feedback I think, and we have done that in different kinds of studies, seems to have some beneficial effect in retention.

And I think when it comes to providers just to restate what people have said I mean the bottom line is if it is a clinically relevant question as Lew said the epileptologists really want to know the answers. And so if you can keep them in the loop about we are working on it, we are working on it and then identify by thank you the high rollers or the champions I think that also has a self-reinforcing effect.

DR. SCOTT: Okay. We are going to do questions or comments from Dr. Chambers and then Dr. Holmes and then we are going to move on to the next question.

DR. CHAMBERS: I think this falls into

this topic area but I was thinking of is there a way that we can think out of the box about how the FDA website could function and not just as a place where people go and find out where a registry exists. But actually to facilitate then getting the person who goes to the website in contact with that registry. So I am thinking of it could you go in and enter a drug, a disease and be able to search on the website a match to a potential pregnancy registry and then actually have an email go out that provides information to that registry about that provider or that patient in some fashion that was HIPAA compliant.

The CTSAs have a thing called researchmatch.org that is run throughout the United States that allows patients to register in it with certain characteristics and then people who have IRB approved protocols go in and enter their information into researchmatch.org and if the patient meets the criteria then they get an email saying that you might qualify for this study; would you be interested in hearing more.

They open up the option of being contacted and then the researcher gets that contact information and can contact the patient to see about enrolling them. And that works nationally. So I am wondering if there could be a way that you could maximize use of the FDA website.

We were talking earlier about FDA being perceived as a trusted source without different objectives in mind would that be sort of a one-stop shop that at least a provider or a patient can find out yes, I might qualify for this particular registry and then give permission to be able to be contacted.

MS. THOMAS: I am not sure about the capabilities of the website but it does raise some issues in terms of if you do search drugs at FDA and get information about it is there something that could be added there that says there is a registry for this particular drug, I don't know if they will have the capability of sending an email but at least of having something there. But I will definitely check into it.

DR. SCOTT: Dr. Holmes?

Okay.

DR. GREENE: Just quickly, Mike Greene. On the FDA's website now when you go to the registry, the list of registries you can click right through to the registry's website. And there you can get whatever information and/or supply any information to the registry depending upon on how their website works. So the FDA is sort of facilitating that already. So you can click right through. The web address for the registries are right on the FDA's website.

MS. THOMAS: Yeah. I think this was in reference to if you go somewhere else on the FDA website and you just search for something about a drug if we could take you back to the registry page and then connect you that way.

DR. SCOTT: Okay. So we are going to move on to the next question which is: Discuss the role of the FDA in communicating information about pregnancy registry. We want you to consider in your comments recommendations for the FDA's

Office of Women's Health webpage and other methods that FDA uses to communicate information about the existence of a pregnancy registry.

And I want to start off by asking the first question to the panel. I notice that in some of the presentations people talked about how they used the information that is currently on the FDA's web page for pregnancy registry. Some people mentioned that they used it as part of their recruitment tools. Other people viewed it as a FDA clearinghouse so to speak for pregnancy registries. And so I just want to get more information from the panel in terms of how you use the information that is on the web page and what your recommendations are for us to improve it because as you saw from the presentations this morning it is not a comprehensive list. And so we want to make sure as we move forward we implement changes so that it is more useful for you.

DR. GREENE: Mike Greene. So let me ask a question in response to that question. How do the registries get on to the FDA's list of

registries now? Do the registries have to approach the FDA? Does the FDA -- how does it happen?

DR. SCOTT: So the registries that are listed come from two sources. Some of them are post-market commitments and post-market requirements so that we are aware of them within FDA and then they are cleared and they are put up. Others are voluntary in which the company approaches us and say I have a pregnancy registry and I would like you to post it on the website. And we take that information and we consult with our colleagues and CDER to see whether or not it fits the definition of a pregnancy registry and whether or not we should post it.

But that is an interesting question because on the website we don't distinguish whether it's post- market commitment, post-market requirement or voluntary. So is that something which would be useful for everyone to know how we put things up there, what categories they fall in, how do you want us to sort? Right now it is sorted by

disease and you could also sort by actual product listing. What is the best way to communicate this information to you?

DR. GREENE: This is Mike Greene again. So with that then as background I think one of the themes that has run through the discussion is who is your audience okay. So is your audience providers or is your audience patients or do you need both and if you are going to do both can you reach both with the same approach. And if your audience, who are your customers, if your audience is providers do you want it to be obstetricians or do you want it to be the neurologists who are prescribing anti-epileptic drugs or do you want it to be gastroenterologists and infectious disease docs who are prescribing the Ribavirin for HepC. So and it is likely that one size is not going to fit for all, okay. And that you may need different ways to attract doctor's and provider's eyeballs as compared to patient's eyeballs on your website.

So I was struck by the fact when I saw

the presentations today that there were two different ways of finding your way to the registry. One is just going to the FDA CDER site which is the way I did it. And the other is to go to the Office of Women's Health Site. And it seemed to me there was slightly different content on the two different sites.

DR. SCOTT: So that is something that we can look into because I am not aware of the differences between the information. I would think that it should link to the same webpage.

MS. THOMAS: I am not sure what CDER page you were referring to. If it is just that you went through the drugs tab and it took you back to our list. But the page that we show basically there are three different pages that are all within the same section. And the main page is the page with the woman on it and then there is the main list page and then there is some more -- a general information page. But they are all in the same regardless of whether or not you come through the drugs tab or you come through the

Office of Women's Health tab it takes you to the same place.

But one of the things that you did raise is something that we are considering with the restructuring or reorganization of the website is that when you come to the main page having the button that says for providers and a button that says for patients and it takes you to slightly different information. You still may end up on the same list page but where you start off would be a little bit different and the way the information is framed will be different if it is for the provider or the patient. But I think one of the things that you raised in terms of the specificity for the different types of providers we may not be able to be that nuanced in that one website but at least having a separate entrance point for providers is something that we are considering.

DR. HERNANDEZ-DIAZ: Perhaps something to keep in mind for who is the audience perhaps neurologists or epileptologists or HIV infection disease doctors know about the registries for this

particular medications because they have been around for a long time and they are known to have potential toxicities that result in that. But perhaps this FDA website will be particularly useful for more of a general audience of OB/GYNs or primary care providers that may have to prescribe different medications occasionally to pregnant women. And perhaps the alert we were talking before that the represented having electronic medical records give an alert, a yellow light, that could include the link to the FDA website where the provider could find and access information about many registries in case these prescribers have to prescribe many different medications to different women with different conditions. So just to keep in mind when designing it.

DR. SCOTT: Any other comments?

So can anyone think of any other groups or organizations that we could potentially target to increase awareness of the web page?

DR. GREENE: Mike Greene. So I don't

think that you will be able to find one group that you can contact about the webpage for all of the registries. I do think, however, that there are patient groups that find -- that patients find each other on the web as interest groups if you will and those interest groups whether it is anti-epileptic patients or whether it is patients with cystic fibrosis or other disorders those patients do find themselves and do have their websites and chat rooms on the net. And you can target them for their registry rather than all registries.

MS. BECK: I am curious about the pregnancy media, both digital and traditional print. I would assume that they would be very interested in having information about a centralized source and again I have done little bits here and there but I am wondering if there is an opportunity for a centralized effort with Fit Pregnancy, The American Baby, you know the laundry list.

MS. CHAMBERS: We had talked earlier about the possibility of proactively sending out a

text for baby message at the first contact when a woman signs up in pregnancy that says go to the FDA website and having a link there to see if you qualify for a pregnancy registry.

MS. COSTER: Actually for other groups you are asking about contacting is the P&T committees. They are the ones that really own the ability to change the electronic medical records for drug warnings and vaccine warnings. So they are a good organization as well as your patient safety community because usually have a patient safety officer at a hospital who kind of goes to all the other specialties and can transmit information; so insuring that patient safety officer is aware that there are registries that the P&T Committee is aware of the registries; it helps them then decide as a hospital organization how are they going to disseminate and warn patients about information.

DR. SCOTT: A question that I have is outside of the registry process, does the panel have any recommendations on how we can encourage

patients and prescribers to report information on drug exposures during pregnancy. Outside of the registry process, do you have any recommendations on how we can encourage patients and prescribers to report information on drug exposures during pregnancy?

DR. MITCHELL: Are you talking about just the fact of an exposure or link to an outcome?

DR. SCOTT: Link to outcomes. So we know we have the Med Watch form and you report information there. Is there anything else to capture some information?

DR. MITCHELL: I guess I would pose the question of whether does FDA want to do that? The value of those spontaneous reports is minimal at best. And I frankly would see that as a distraction and perceived as competitive to the registry effort which is interpretable.

DR. SCOTT: Thank you.

Dr. Holmes?

DR. HOLMES: Yeah, I think to echo what

Alan said there are two well documented examples of where studious review of the adverse event reports has led to spurious publications of alleged teratogenicity that required a lot of effort to dispel. And so the FDA system not only didn't work but it caused harm. So there is no sense in encouraging it.

DR. SCOTT: Okay. Any comment or questions from the people on the phone.

DR. SAHIN: All right. So we discussed a lot of topics today and I am just going to try to do a high level recap of some of the key messages that we received.

So quickly to go through some of the key messages: We need to be clear about the information that can reasonably be obtained from a registry; taking into consideration issues like the sample size, the power of the study, and the outcomes that are being assessed. Marketing efforts need to be established from the get-go of the pregnancy registry and whatever resources and

money are spent in terms of marketing, that it is really money that is well worth spending to raise the awareness of the pregnancy registry. There was a lot of discussion about prospect of enrollment and how the definition is changing as prenatal diagnostic tools advance and so this needs to be taken into consideration when data is analyzed and submitted to the FDA. Inclusion and exclusion criteria need to be clearly defined. Comparison groups need to be appropriate for the study population. And we also heard that FDA needs to develop standards for specific surveillance methods and increase its standards in terms of what it asks for for a post-marketing study.

This afternoon there was a lot of discussion on the use of electronic media to raise awareness and increase diversity in these studies. Use of electronic medical records alerts; notify health care providers of a pregnancy registry. There was a lot of discussion regarding the need to engage the patient to improve enrollment into a

study and also keep them engaged and improve retention in the study. And there was also discussion about the importance of providing feedback to the patients in terms of the study findings because a lot of patients do participate for altruistic reasons and for them it is important to feel that they contributed to the study. But there was also discussion about the importance of the health care provider as well as it is the health care provider who often refers the patient and a health care provider's encouragement or interest or support of a patient to enroll into a registry has an important impact on whether or not the patient will enroll into the registry. And there was also discussion about the importance of identifying health care provider champions to spread the word about a registry.

So I may not have captured all the points but those were some of the key messages that we received. So it has been a great day; a lot of stimulating discussion.

And thank you very much to everybody,

all the panelists, and all the members in the audience including all the people who made public comments. And we really appreciate everybody's participation.

Thank you very much.

And we look forward to seeing you tomorrow morning.

MS. MOYER: Tomorrow morning we start at eight o'clock.

(WHEREUPON, the meeting ended for the day.)

CERTIFICATE OF NOTARY PUBLIC

I, ERICK MCNAIR, the officer before whom the foregoing deposition was taken, do hereby certify that the witness whose testimony appears in the foregoing deposition was duly sworn by me; that the testimony of said witness was recorded by me and thereafter reduced to typewriting under my direction; that said deposition is a true record of the testimony given by said witness; that I am neither counsel for, related to, nor employed by any of the parties to the action in which this deposition was taken; and, further, that I am not a relative or employee of any counsel or attorney employed by the parties hereto, nor financially or otherwise interested in the outcome of this action.

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ERICK MCNAIR
Notary Public in and for the
State of Maryland

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I, CHERYL LaSELLE, hereby certify that I am not the Court Reporter who reported the following proceeding and that I have typed the transcript of this proceeding using the Court Reporter's notes and recordings. The foregoing/attached transcript is a true, correct, and complete transcription of said proceeding.

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