data, or it would just take too long and be too costly, again maybe suggesting that one type of study shouldn't be used to answer all types of questions.

There was also the thought that perhaps too much additional data was being requested by the guidelines, I guess in a sense echoing this idea that surveillance of the many implies not very much information, whereas intensive follow-up really is meant to be restricted to the few.

They also alluded to the fact that there were many difficulties in generating enrollment to look at main associations, much less to look at subgroups; that there was an extreme difficulty in identifying appropriate control groups, especially for drugs taken for chronic conditions.

And from a more legal point of view, there were confusions about regulatory reporting requirements. At least at a place like CDC, a lot of whether something is surveillance or something is an epi study is really a legal question in a sense because if you're a surveillance system, you don't need IRB clearance and the same if you're an epi study. So, those legal questions pop up in a number of different frameworks.

I think we're going to hear a talk next about the wonders of centralized registries. I'm not going to

tilt one way or the other here. But there was an interesting quote in one of the papers. "To date, pregnancy drug registries have not detected any previously unknown teratogens." Obviously, a complete failure. Let's do away with them? No, I don't think that's quite the answer.

I think a better way to look at this is to say that the background work in setting up a registry in many cases probably has provided all kinds of useful information. It has provided estimates of usage of drug during pregnancy. It has provided experience in methods of locating and enrolling women being in registries. Certain drugs I think have an easier time of this. If you have a drug which is being used in a more identifiable group, for example, women who are HIV positive, women who have diabetes, you may have built-in mechanisms to try to find those people, but I think as you've gone about this, you've become much cleverer about the way that you find out who are the women that are taking these drugs.

You get experience by running the registry. You learn to recognize what are appropriate data collection sources. If you are going to try to get at a variety of types of outcomes, you become more savvy about can birth certificates tell you what you want to know. Can cancer registries tell you what you want to know? Can birth

defects registries tell you what you want to know, or do you need to go directly yourself to the medical record or to the person and find these things out?

You also begin to learn what data elements are collectible in the sense that people will answer you or that they, for example, will be available in a medical record or that people will tell you in an interview. What's my job? None of your business.

Then the experience from actually using the registry data. If nothing else in the sense of the prospective women that you have put together, you certainly have some descriptive data on the level of risk.

Also, as you go about trying to see whether there is something beyond using general population data, I think you also learn a lot about whether good controls are available. I think, for example, in the area of HIV positive women, it's very difficult to identify a good control group and possibly impossible.

I think one thing you may find out in this area, though, is that you may have to use other drug groups as your control group. You may not like it, but what you may end up doing in some sense is comparing drugs rather than comparing a drug to no exposure.

I think lastly I want to emphasize I think one thing that is almost always overlooked is the importance of

negative findings. Oh, we didn't find any cases. Boy, what a bummer. Nobody died. It's good. I mean, it's good when horrible things don't happen to good people.

You do this registry, you do this surveillance system, you do this epi study, and you see that in a series of N pregnancies, there were no observed cases of outcome Y. If N is 10, that's not very impressive, but if N is 100 or 500 or 1,000, you actually can make some fairly strong statements about the absolute level of risk in this case.

Sort of a general rule of thumb, when you observe 0 cases out of N events, an upper 95 percent confidence bound for that absolute risk is 3 out of N. It doesn't mean it's impossible, but it means if you view of 1,000 pregnancies with no events, you tend to doubt background risks of greater than 3 out of 1,000, for example.

So, in conclusion, I hope that I have been somewhat convincing in telling you that to evaluate specific exposure-outcome associations in a timely and useful manner requires, in most cases, a great deal of background information which in most cases will be the hard work of someone else's results.

You need infrastructure and a lot of the problem will be who's going to supply that infrastructure. Is it going to be a drug company? Is it going to be the

government in some sense?

And it takes time. Maybe you think it's ironic to say it takes time to do a timely response, but I mean time in the sense that you need to have started a long time ago to have a timely response now.

Finally, don't think that all associations can or should be evaluated in exactly the same way. Again, the rareness of an outcome certainly dictates how you should go about studying it and also your ability to characterize it. It also dictates how you should go about studying.

Finally, don't underestimate the importance of negative studies. You've got a negative study, you've got a negative study, they've got a negative study. If you just got together, you'd have a really positive outcome at that point.

So, thank you.

DR. GREENE: Thank you.

(Applause.)

DR. GREENE: Questions or comments regarding Dr. Rhodes' presentation? Don?

DR. MATTISON: Since Dave Erickson is here and you've had experience with multiple types of databases, surveillance systems, whatever, maybe the two of you could address the issue of the usefulness of combining or strategies for combining individual state birth defect

surveillance systems in ways that might help underpin registries that would be established by manufacturers to try to better characterize risk of drug exposures to pregnancy outcome. How can the existing systems be used in any meaningful way?

DR. RHODES: Let me make a general comment and then I'll defer to Dr. Erickson for the specifics of that.

I think in some ways it's certainly very attractive to have centralized registries in the sense that you now have a common infrastructure, if you will, that group A doesn't have to build an infrastructure different from group B, different from group C. There certainly is a savings and a synergistic effect in that regard.

However, I wouldn't want people necessarily to be fooled into thinking that, oh, and now we're going to get more people who are exposed to a certain drug necessarily unless there's something about the centralized registry that has more clout to go out and find people or just more smarts about doing it. For example, if in the HIV/AIDS surveillance activities we can identify a substantial portion of women who are HIV positive and have been pregnant, I don't see that a centralized registry of all kinds of other drugs is going to do any better of a job for us than we can do for ourselves in that regard. But if you have a drug that has no home or an outcome that has no

home in that sense, I think all those kinds of exposures or outcomes can find a common home and benefit greatly from it.

DR. GREENE: Did Dr. Erickson want to comment on that?

DR. ERICKSON: I think Phil did a good job of answering it.

DR. GREENE: Okay.

DR. WIER: I wonder if you could comment on whether exposure registries versus outcome registries are more suitable to be centralized. We hear in discussions people using the word registries, but I see them as very different animals. I'm not sure that they're both equally amenable to centralization.

DR. RHODES: Certainly one attractiveness of a centralized exposure registry is when there is the likelihood that people have multiple exposures, and that's an important piece of information either in terms of that it's the combination that does something that neither one can do by itself or one is the control for the other. If I'm running registry A and you're running registry B, we may never get that information together.

The other side of it is that I think it's also a function of how long of a list of exposures do you have, how long of a list of outcomes do you have. Nobody owns

outcomes, but people do own exposures in the sense of a drug company or multiple drug companies own exposures.

For example, in the context of the Vaccine Safety Datalink and the varicella vaccine, one of the study sites, one of those HMOs, has an ongoing -- I'm not sure if it's ongoing, but it was an extensive ongoing surveillance system for varicella vaccine paid for by the manufacturer that was apart from the Vaccine Datalink study. But they did an even more active follow-up because they were also interested in breakthrough cases and various things like that.

So, in those contexts I think the difficult things about these exposure registries when they are really owned by some entity, whereas if it's environmental exposures where it's harder to point to a particular entity. So, I think administratively there is this extra burden to overcome of how do we get 10, 12 groups together to talk about all these exposures.

I think that exposure registries -- for example, a sister agency to CDC, ATSDR, has exposure registries, but they seem to expend an awful lot of time getting exposures, but they haven't really got to the outcome side yet. So, I think you have to think carefully. Well, I'm going to get all this exposure data. What outcome sources am I going to compare it to?

Now, in the case of the Vaccine Datalink, it's obvious you've got everybody who's in the same medical system, the exposures and the outcomes are coming more or less from the same system.

DR. GREENE: Jan?

DR. FRIEDMAN: One advantage of centralized exposure registries from the point of view of people who contribute the information to them, that is, the physicians and the health care providers, is that you would just have one number to call, you'd have one place who could provide the information from them if you're trying to get information too. I think that that in itself would increase the amount of data that you would get. It would just make it easier. If there was one phone number, one web site, that's where you went and you didn't have to figure out whether this particular drug was made by company X or it didn't have a registry or it did, it just would facilitate it. Since you're depending on a passive, voluntary system to start the process, you want to make that easy.

DR. RHODES: I think you're right in that sense except that the person you're going to get a hold of is going to have to be more generic in their knowledge.

DR. FRIEDMAN: The person is the doctor who prescribes the medicine.

DR. RHODES: No, but I mean in the sense of when you're interacting with the registry, you're going to be getting a person who's more generic about their knowledge.

DR. FRIEDMAN: That's the same thing whether it's the manufacturer or OTIS that's providing the data. They're still interacting with the same data sources.

DR. RHODES: The other down side, though, of a centralized registry can be that -- take, for example, the antiretroviral registries. They actually are one of the few examples where it's run by a consortium of drug companies. One could think of a lot of questions you would ask in this context that are of no interest to a general registry. In other words, there still has to be some way of having very specific questionnaires for certain classes of drugs. So, I think even if you have a centralized registry, there's going to need to be some specialization within that centralized registry and people are going to be responsible for certain portions of it.

One way of imagining a centralized registry is if I'm working for the registry, I can go off and do any number of drugs and I'm not specialized in any particular exposure. I'm not sure that's going to satisfy groups that want very specific information.

DR. FRIEDMAN: I agree completely.

DR. GREENE: Don?

DR. MATTISON: Given your experience with FARS, the Fatal Accident Reporting System, do you think it would have been better had it been done by Ford and GM or in a centralized, non-manufacturing dependent way that it's currently structured?

DR. RHODES: I think it's just fine the way it is. I think that independence is good. One topic that has come up a number of times in the Vaccine Safety Datalink study is, is there a way for the vaccine manufacturers to participate in a way that doesn't taint it in some fundamental fashion, which is sort of an ironic question given that these are sites where drug vaccine trials are done all the time and special follow-up studies are done all the time directly related to the manufacturers. So, it's a funny question in a way but I guess it's not so much the HMOs being involved with the manufacturers, it's the government being involved with the manufacturers is the real question in getting back to your comment about FARS.

While the source of funding -- in the government, these things can go up and down and you're worried your surveillance system is going to go away at any moment and where is the funding for next year. Having an ongoing source of support from the manufacturers would be comforting. For example, in that study, they have not

found a way to do it in a way that people feel comfortable about.

DR. GREENE: I'd like to come back for a second to the exchange that you and Jan just had a minute ago about the advantages and disadvantages of a centralized system and familiarity of the people at a centralized system with the individual agents. In that exchange, was there a little bit of confusion between the reporting function and the reporting out of the results to the individual providers for use in counseling?

DR. RHODES: Well, I think in the sense that if the place that receives reports has any function of providing information, whether it be just on the phone -- what can you tell me about something -- if you're providing written reports, then obviously I can go to the shelf and you can go to the shelf. We're getting the same report.

But to the extent that there's a personal exchange of information, I think when you call up the antiretroviral registry, you hope they know something about antiretrovirals. You call up the centralized registry, well, that's not my expertise. I know about anticonvulsants.

DR. GREENE: And that's an area that I think we need to come back to again later I think maybe, those two different functions: the data collecting and gathering

function versus the sort of digesting the data and helping clinicians use the data in counseling.

Allen?

DR. MITCHELL: Just a couple points. One, I thought that we were going to come back to it, so I was going to defer my comment. But I think it's not only important to separate those functions. And I agree with Jan. I think it's very useful to and it relieves a manufacturer or some information response burdens that actually could constrain the research activities. We've heard how the manufacturers are constrained in what they can say, what they can do, getting a control group, for example. A centralized registry would obviously, if it's done in a reasonable way, have the opportunity to do appropriate research rather than being constrained in some other ways.

But the other point that I wanted to respond to, Phil, was that I think the issue of centralizing state-based activities, there are some strengths to that which weren't mentioned. I think the CDC Centers for Excellence is a perfect example of enhancing not only the power of eight different population-based registries, but centralizing expertise and learning. I think if each state were to try to duplicate what is being done on a centralized basis, first of all, it wouldn't be very good

and it certainly wouldn't be as efficient.

Related to that, I think that there is some confusion in the discussion when we talk about exposure registries versus outcome registries and when one is appropriate and one is not. I think when you have a drug that's reasonably commonly used, then case-control surveillance is a very powerful way of responding to questions. Where you have a drug that's infrequently used, case-control surveillance is going to be pretty useless. So, again it's an issue of the segregating the design to meet the question that's being asked.

DR. RHODES: I would certainly agree with those comments.

DR. GREENE: Yes, please.

DR. RHODES: I would just make one additional comment. One strength of the Vaccine Safety Datalink study is that there are four HMOs involved that have their own active research organizations and that evaluation studies that are conducted from that data are not just done by CDC. They're often done by the HMOs themselves or in some collaboration. So, having those groups take part in that study and also colleagues from the FDA, having all those different groups involved has made it a much stronger effort.

DR. WEISS: Your talk and Dr. Mitchell's

comments really crystalize something Dr. Andrews and I have spoken about previously, and that's maybe where we should be more careful with our terminology and that will help us come to some better maybe consensus on some of these questions. I think we're throwing the word "registry" around way too loosely and are talking about probably the entire spectrum from outcome-based registries, such as a birth defect registry, exposure-based surveillance of cases, as we heard about from Merck, to longitudinal cohort studies where you have an exposed and non-exposed cohort, maybe disease-based such as the antiepileptic registry, then to targeted case-control studies.

I think obviously when, how many, whether or not it's feasible, and when we should ask to do them based on what we know a priori I think is really going to drive what we're going to do and how we're going to do it. I think maybe we need to be really clear when we discuss these issues what we are trying to do and what type of study we're talking about.

DR. GREENE: If there are no other questions, I think we'll move to the last speaker of the morning then please, to Dr. Jan Cragan from again the CDC.

DR. CRAGAN: One of the questions for discussion this afternoon refers to a centralized pregnancy registry, and we've already started that a little bit here.

I'm going to explain some of the background of the current registries from CDC's perspective and how we came to be talking about a centralized registry and what we really mean by that. This will focus on registries for drugs of undetermined teratogenic risk.

Elizabeth Andrews explained yesterday how the acyclovir registry got started in 1984, and this really came out of the activities of the epidemiology department at what was then Burroughs Wellcome Pharmaceuticals. It dovetailed very nicely with what CDC was trying to do in terms of monitoring treatment for herpes exposures.

Members of the Birth Defects and Genetic Diseases Branch served as birth defects consultants on the advisory committee for the acyclovir registry, and because of the success of that registry and subsequent efforts, we rapidly found ourselves serving on, when acyclovir was active, a total of seven registry committees, each of which met maybe a couple of times a year. We ended up sending staff to maybe a dozen meetings each year, many of which had duplications of discussions and sometimes duplication of efforts.

We found ourselves repeatedly in discussions about wanting very much to promote and encourage these kinds of proactive registry activities by the pharmaceutical company and realizing that there were

limitations to the methods and the type of data that they collected, and they weren't really generating the information that we thought was needed. To do that, would require an active collaboration between the patients and their physicians, the regulatory agencies, the pharmaceutical industry, the public health agencies, the private consultants, and all the varying groups.

Just to review a little bit, these are the basic strengths of the registries that we've talked about over the last couple of days. They represent a shift in the focus of the pharmaceutical industry toward actively monitoring for adverse effects of drug use in pregnancy. I'm not sure it's really a shift so much as it's an emphasis on actively looking for problems with the drugs.

The prospective nature of the ascertainment reduces the selection bias that's inherent in adverse event reporting and allows calculation of the risk of adverse outcomes. So, it's a next step, if you will, in the evaluation of pregnancy risks.

The registries have an increased statistical power to identify defects resulting from individual drug exposures because they enroll only exposed pregnancies. The advantage of a cohort study is its ability to evaluate rare exposures.

Some of the limitations of the methods are that

the registries have difficulty in obtaining sufficient sample size to evaluate changes in individual defect rates, as we have seen several examples of. A cohort study is not efficient in evaluating rare outcomes.

We've talked some about the lack of a control group. The Glaxo Wellcome registries state that they're worldwide registries and they will take case reports from any country at least where their drugs are marketed. In reality, it's not spread uniformly across those countries and they get a lot of reports from the U.S. and Great Britain and Australia and very few from other areas. So, it's very difficult to know what the actual population is that's giving rise to the cases that are included in the registries.

Elizabeth mentioned yesterday about the paper included in your background materials that compared the registry birth defects ascertainment to that of the Metropolitan Atlanta Congenital Defects programs. This is a retrospective, hospital-based ascertainment of birth defects among newborn infants in Atlanta. We use that as a comparison because we thought it was the most comprehensive comparative group we had, but we'd be the first to agree that that's not the appropriate comparison group for the registry methods because they're so different.

We've talked some about the quality of the

data, both the difficulty in identifying, pinning down the exposure in pregnancy and trying to link that to times of specific organ development and the difficulties with outcome data, particularly when the outcomes are obtained from obstetricians who have very limited contact with the infant.

Then there are the confidentiality issues, the ethical issues, the issues around protection of human subjects and obtaining informed consent that are not dealt with uniformly across all of those registries.

So, with that background, it became apparent that it's impractical to set up an individual registry for every drug or every class of drugs that we want to monitor. So, in January of 1999, a little over a year ago, CDC and FDA began to discuss the long-term future of these activities and whether there might be a way to combine or centralize the efforts. We thought that centralizing efforts might allow more efficiency in reporting by the providers. It might provide more consistency in analyzing the data and perhaps allow comparison of defect rates among different exposures or of one exposure to all of the others, some of the types of things we've talked about here.

It soon became very clear that the issues involved were too complex for us to resolve and that what

we really needed to do was to bring together all of the people who would be involved in or affected by a registry to do some brainstorming about how and whether it might actually work.

The last item in your packet of background materials is a draft proposal for a workshop to develop a centralized pregnancy registry. The last page of that proposal lists the agencies that had input into its development and into the proceedings for today's meeting.

The basic considerations for a central registry are these.

First, we have no preconceived idea of what a central registry would look like. This needs to be defined. We've said that the term "registry" is a bit of a misnomer or very much a misnomer. We aren't just talking about doing what the individual registries do on a larger scale. What we'd really like is to consider whether there's a unified approach or a unified plan that could be taken to address some of the issues that have been raised yesterday and this morning.

Perhaps the mechanism for studying various exposures and outcomes exists sufficiently and what we need is coordination of programs that can bring together information that can answer some of these questions. Perhaps what is needed is further development of existing

resources so they can address a wider range of exposures and outcomes. How do we go about setting up the hierarchy of studies to answer different questions that we've talked about?

In her opening comments yesterday afternoon, Sandy Kweder asked you to be creative and to think outside the box. When we talk about a central registry, that's really what we're asking you to do in thinking about these approaches and how we can have an organized way of addressing the issues.

The data to be collected addresses not only which drugs to monitor and which outcomes we need to evaluate, all drugs versus some, all defects versus some, miscarriage rates, low birth weight, long-term neurodevelopmental outcomes, but also how the data should be analyzed.

If a signal of concern is generated, what should be the next step in its evaluation and who's best to do that? Can we nest case-control studies within the surveillance to address specific issues? In which situation should we begin with a case-control approach? Who is best to conduct the different studies and how do we coordinate them? What's the best way to assure the objectivity and the scientific integrity of the findings and who is best to interpret them and disseminate the

information? All of these are included in what kind of data should be collected.

Then how should a central registry be administered and funded? We're not saying that CDC itself is going to do this or that FDA itself is going to do this. What we'd really like to talk about is what's the appropriate role for industry and what's the appropriate role for the government and what's the appropriate role for the private sector and who should interact with the patients.

How can we uniformly and consistently address the ethical and human subjects issues? What's the most efficient way and the way that's most acceptable to those involved in doing this? These may be different for different approaches, but how can we get them all together?

These are the kinds of issues that would be addressed in a workshop to design a pregnancy registry, and you'll see them reflected in the discussion questions for this afternoon. But we aren't asking you to design a central registry today. It's really the last issue that we want to talk about, and that's is a central registry really worth the effort.

We felt it was important to take a step back and look at the overall picture. Is a central registry something that there's interest in and support for? Is

this something that you can take back to the groups and the organizations that you represent and work with and generate ideas for and begin to plan?

We'd like your advice on where and how effort should be spent to improve our knowledge about the risks of drug use in pregnancy, and what we really want help with is what is the appropriate next best step and how can we all work together to make that happen. So, these are the things we'd like you to keep in mind during the discussion this afternoon.

Thanks.

DR. GREENE: Thank you.

We'll now have questions and discussion about this presentation, please. Yes, please.

DR. HAMMOND: So that we don't reinvent the wheel, are there other countries in the world that have this type of central pregnancy registry? Has this been reviewed?

DR. CRAGAN: I don't know of one that combines well the private sector and the government sector, and so there are central monitoring systems in some of the European countries, but I don't know. Sandy, perhaps --

DR. KWEDER: I don't think that there are any systems specifically like this. There are independent efforts that do this and there are countries, particularly

where there are national health systems that automatically capture prescription information and other health record and outcome information that can generate signals and do this sort of thing but they're based on health records.

DR. GREENE: Jan?

DR. FRIEDMAN: Jan, I wonder if it might be useful to take a step back from the proposal to have a central registry and ask first whether there's consensus between the FDA and CDC and the public and industry and whoever else is involved about the need to have better information about what the effects of these drugs are on pregnant women and their children.

I think the answer is unequivocally yes, and if it becomes unequivocally yes, then I think there's an imperative to do something better than we're doing now. That may help to drive whether it's a central registry or whatever but may help to drive some solution. It's hard for me to imagine anyone being satisfied with the situation we have today or not wanting to do better. I think if we can get a consensus on that principle, it would help us move forward.

DR. CRAGAN: Yes. If you look at the discussion questions for the afternoon, that's what they're trying to address, is what's the status of our knowledge, what do we need, and how can we generate some of that.

That's exactly what we need.

DR. GREENE: Dr. Rodriguez?

DR. RODRIGUEZ: Yes. I'd just like to address the question of whether there has been experience in other countries. Other countries have had experience in this area, and the Hungarians have had a surveillance type system where they then conducted case-control studies to look at associations and risks.

DR. MITCHELL: I think that there really is a compelling argument for a centralized approach for a whole variety of reasons, many of which have been alluded to.

But I think that, again, to bring the model of the CDC Centers for Excellence in Birth Defects Research to the fore, the experience that many of us have had in working in that project, which involves eight states which might be the equivalent of eight companies conducting their independent registries, has really been an eye-opener, even for some of us who think of ourselves as older folks in the business.

The number of questions, the number of issues requiring resolution are just legion and they're even greater than what one would anticipate in reviewing a paper that comes out of a registry. I think the arguments about the need for a common infrastructure, the arguments for efficiency, the arguments for objectivity, and also the

arguments for relieving industry -- and I don't know how industry would relate to this -- of a very narrow burden that is very burdensome, the problem of controls and whether they can legitimately enroll subjects who are exposed to other drugs. The problems of comparisons, the problems of follow-up. I think from a public relations standpoint, an independent registry or follow-up program could have great impact. It could be incorporated into medical practice, as Jan was talking about, having an 800 number, a single number.

I can think of just an infinite number of arguments in favor of a centralized registry. I'm hard-pressed to think of any arguments against it. I'd actually be curious, if it's not out of order, to ask for some thoughts about why a centralized registry might not be the way to go.

DR. WISNER: It's a slightly different point but it has some relevance to your question. And that is, we've talked about patient privacy and informed consent and patient confidentiality, but we haven't looked at again what may be a parallel process for physicians. This is what I see in a number of talks that I do that are physician education talks about medication use in pregnancy, and that is they all want more information about use of medicines in pregnancy, but they don't want to be

the one to contribute the patient that helps find the association with a negative outcome. So, what they ask is, gee, what kind of risk do they incur by providing information about patient exposures to a registry when the agenda of the registry is in fact to make associations with negative outcomes and what kind of legal ramifications might they incur.

So, I think some thought to protecting the physician's confidentiality or some way to address that so physicians aren't worried about making those reports would be helpful and would be one argument against reporting to a centralized registry that physicians might make.

DR. GREENE: When you say a negative outcome, do you mean absence of disease or presence of disease?

DR. WISNER: What the physicians are basically saying is the reason that registries are done is because of concerns about negative outcomes either for the moms or the fetus, meaning reproductive outcomes, so that they're reporting an exposure and it's possible -- in fact, it's the intention that those exposures would be looked at for their association with events that could become the focus of a legal case.

DR. MITCHELL: If I could just respond a little bit, Kathy. My own notion would be that it would be a patient-based registry rather than a physician-based. The

physicians would clearly be the learned intermediaries in terms of encouraging patients to enroll, but it wouldn't be too hard to envision an encounter in an obstetrician's office which ends at the first prenatal visit with, by the way, I'm taking part in encouraging more understanding about drugs in pregnancy and there's a telephone out in the lobby. If you wouldn't calling that 800 number and they'll talk to you about how you might participate in this and improve life for all of us. There are distinct advantages which may be a subject of another discussion of why it ought to be based on the pregnant woman rather than the physician, consent and OTC and other exposures among those.

I think the companies can bring tremendous marketing skill to bear on this because it really is a marketing issue. As we talked about yesterday, you want to change the way physicians and the public think of this activity. Instead of as an indictment, it's really an attempt to improve understanding.

I think if practitioners can be educated, if there can be some kind of either -- it may be fantasy to talk about liability protection, but some kinds of incentives, perhaps CME. There are all sorts of creative ways of rewarding physicians.

In one study we did -- it has nothing to do with pregnancy -- a randomized trial of ibuprofen in

children, we enrolled 1,700 doctors across the country. Part of the incentive was simply giving them a certificate which they could put up in their offices which says we're taking part in research that's going to contribute to children's health. And they valued that. So, I don't think we should underestimate the interest that physicians have in improving patient care through this kind of activity.

DR. CRAGAN: Yes, I agree. If I can just respond. When we talk about confidentiality issues, most of the discussion here has been about the patient, but it really goes to all levels of people participating or advertising the registry.

One of the reasons we wanted to have primary obstetricians and patients involved in planning what something like this might look like was to get their input on how this can work in their practices and with their patients and how do we get their colleagues interested and what kinds of mechanisms would work.

DR. GREENE: Dr. Rhodes, did you have a comment that you wanted to make?

DR. RHODES: I was curious whether you had contemplated the role of large administrative databases like the Vaccine Safety Datalink in conjunction or sort of constituting such a registry or if the model was that it's

really women who report themselves or the physicians report the women, and whether in conjunction with that, you would want some sample of pregnancies that didn't report themselves.

DR. CRAGAN: Yes. Like I said, we have tried not to have a preconceived idea of what this would look like. We wanted to get input from people about how it might work best, and it may be that there are existing databases that can be used or can utilize for the future mechanisms to do this.

At the present time, the planning committee for this workshop, if it occurs, is trying to look at focusing a little bit on where we should put the emphasis to try to develop something. But it's very easy to get quickly involved in the details if we could do this and this, this is what it would look like, or we could do that, and I think at this point this afternoon we need to step back and go, well, what are all the different sort of possibilities and what is it reasonable to put emphasis on. And that's certainly one of them.

DR. WISNER: Just to follow up the point that Allen made, I like the idea of having the recruitment be patient-based, but the issue that we'll get into immediately is that the standard has been to confirm the patient's report of exposure by physician records. Now, I

suppose an alternative could be pharmacy records, but I think we're going to end up in a circle back around to having to deal somehow with the physician being involved in that reporting process.

DR. CRAGAN: Yes, I don't see any way around it either.

DR. GREENE: Jim?

DR. LEMONS: Just to follow up on Allen's points, which I think are really focused and good, my first knee-jerk reaction is also that the central registry offers great advantages, one being that it could help distance the manufacturers from this onerous responsibility and also add a lot of the credibility of CDC, FDA in operating such a system.

It was interesting. Last night on the MacNeil-Lehrer report, there were two Georgetown physicians serving expert testimony on two drugs that recently had been withdrawn, one being Propulsid. The whole focus of the discussion and the emphasis was a lack of adequate post-marketing surveillance information and that Congress had failed to provide FDA and CDC with sufficient resources to establish infrastructure over time. So, it really is in the public arena at this time.

But my next reaction is that I guess it depends on what is expected of a central registry because one hates

to negate the value of all of the infrastructures that are currently established. I was talking to Christina because I know Dr. Jones and Christina have experience where in California they're funded by California to do a lot of surveillance and actually measure outcomes, so outcomes becomes part of the expectation. But that isn't an expectation -- I agree with Dr. Sharrar -- it can't be an expectation of the usual what our envisioned surveillance systems are from industry.

So that as specific questions arise, perhaps derived from a large central registry, which would capture much more data, then more focused questions could be posed to utilize existing and evolving infrastructures that might engage with industry in sustaining funding over time, as Dr. Rhodes had alluded to, which would provide a lot of security, but again remove the industry responsibility a step away and provide perhaps greater objectivity and greater efficiency and efficacy.

DR. GREENE: Lew?

DR. HOLMES: This is a perfect time to begin to answer some of the key questions. I don't think you can really be sure a central registry would work until you've sorted out the comparison between the Merck model and the system we have of talking to the women themselves. You've got to settle whether controls can be enrolled, how much

that costs. You need some sense of the budgetary projections.

We find, I think, in the epilepsy registry that the fact that we are helping provide answers that the companies need engages them, and they have a sense of a common effort that has very real value to them. If you suddenly had a central registry, would you bring along that corporate support? Would the women who are already refusing to call because they're afraid of losing the confidential data they feel they have be less likely to call a "central registry," which has a lot of connotations certainly in this country.

I think there are a lot of questions to answer. What it seems like to me is the next step, the obvious thing, would be to begin to have regular discussions at a practical level of the experience of registry A versus B versus C to begin to flesh out what seems to work, where the positive things are, the negative things are because I don't think you know enough to know what a central registry would look like.

DR. CRAGAN: Oh, absolutely. I think in our minds we're not sure that even that kind of model in a very general way is the way we should go or the only way we should go. I'm very concerned about having a plan for some of the special studies that need to be done if there's a

concern or generation of a signal or for questions that we know are going to come up that simply can't be answered by a prospective type registry and to have some sort of plan for addressing those other issues that this general registry format, as it's sort of loosely applied to several different registries now or different companies, looks like.

DR. GREENE: Yes, Don.

DR. MATTISON: I'd actually like to ask another question and again, maybe we need to defer it till somewhat later.

One of the advantages of having a manufacturer collect data on adverse pregnancy outcome is their ability to look at questions of biological plausibility. We don't want registries to be idiot savants, I mean, simply collecting the data without being able to put them in a biological context. I think in the environment that we're operating in now, substantially more is being asked of data in a biological context.

So, one of the questions that I think is going to have to be addressed is how would a centralized registry get access to relevant biological information, receptor binding studies or structure-activity data or potentially highly proprietary toxicological data, endpoint data in culture, for example? Because the benefit really comes

from the biological context that the signal is generated, not simply that there is a signal.

DR. GREENE: Do you have any response to that, or no?

DR. CRAGAN: No, I agree. The more you talk about this, the more complex it gets. I know that there are issues that we haven't even thought of yet. So, really trying to plan it becomes a major task.

DR. GREENE: Jan?

DR. FRIEDMAN: I think there are two obvious responses to that. One is that the registry ought not to be seen as the administrative project but more as a scientific project where the people who are involved are not just doing it because it's a job that they have to do this week, but rather are committed to the data and committed to understanding it.

The other is that in this age of electronic instant communication, a central registry need not be in one place at one time. So, one could see a centralized 800 number or a centralized website that served as the front door, but the anticonvulsant drugs might be housed in Boston and the part related to antidepressants might be in San Diego and some other part might be someplace else, and they all function under a common infrastructure and talk the way that the various states talk to have a common set

of questions, but still had different questions where they're appropriate. I don't think we need to think of a bureaucratic, lock-step kind of thing that's completely insulated from science and insulated from reality to have a centralized registry.

DR. GREENE: Allen?

DR. MITCHELL: Yes, I would second that although, Jan, I don't even think you need to go as far as sort of having a front door with different rooms in the house.

I think that the issue you raise is a very important one, Don, but I really don't think it's a very difficult one to solve. In our Accutane project, which is a very different activity, manufacturer's representatives sit on our advisory committee. It's not very different from your experience where the manufacturer is running the registry but there's an advisory committee of outside experts. I think it is not at all removing the intellectual activity, I would argue it's enhancing it, and because you have at the table different interests being represented, the issue of proprietary information can be dealt with pretty easily I think. I wouldn't see that as a stumbling block at all. I think it's actually an advantage.

DR. GREENE: Other comments before we break for

lunch? Yes, please.

DR. ANDREWS: I think we really need to have further discussion about which drugs would be monitored because I would hate for us to think that we could be casting such a wide net that we would really diminish our ability to get people to the door to begin with because I think when we look at all of the registries that involve someone volunteering to come forward and report themselves or a patient to a registry, that's the fundamental problem. It's how do you get them to begin with. And if we do cast such a wide net, I think it's going to be very, very difficult even though I agree it would be simpler to have one single number. But how do we encourage that reporting?

Or is that the right model? I'd go back to Philip's comment about whether it's possible to use another system that might be in existence to identify and do a better job of full capture of exposed women. For example, using administrative databases which may not be sufficient for answering all of the questions, but could certainly identify all patients within a defined population who have had a pregnancy exposure to a particular drug. That's something can't do right now or we're not doing. But it's certainly possible to use administrative databases as a starting point for identifying all women in a defined population with a given exposure.

Certainly using the model of a database in the UK, the General Practice Research Database, which includes about 5 million people with electronic medical records from 1989, it's certainly possible to identify all women with exposures to certain medicines, and then one can nest various studies within that by going back to the physicians or even contacting women.

So, I would encourage us to think more broadly than just systems which have to get people to come to a door.

DR. GREENE: I just had one question for the epidemiologists in the crowd. When you raised your hand after Don spoke, I was wondering whether epidemiologists get nervous when people start talking about biological plausibility of data.

DR. MITCHELL: Do I have to answer that?

(Laughter.)

DR. MITCHELL: Actually some epidemiologists welcome that.

DR. MILLS: We love biological plausibility.

DR. RHODES: I'm not sure where I saw it, but there was a comment recently that biologists should think about epidemiologic plausibility.

(Laughter.)

DR. KWEDER: I actually had just one comment

that may be a little peripheral to this but I think touches on the concern that Kathy raised about protecting physicians who share information and also the one that Allen raised regarding the interest among clinicians who are out there in contributing to data collection efforts.

I think that those points are very germane to a general issue that has been a focus of great discussion in our agency and I think among other government agencies and in the private sector regarding the Institute of Medicine's report on medical errors. If you listen to John Eisenberg from what used to be AHCPR and now is ARQ talk about what we need to do to address that, one of the things that we at FDA are cognizant of is importance of -- as we look toward new systems for data collection and finding solutions to problems like medical errors or worries about people administering medicines that may not be safe or administering them in ways that may not be safe, we need to create systems that allow people to contribute the information that's out there in the trenches without fears of reprisal. I think that all of that does need to be part of our discussions here.

Should we be thinking about ways to make things a win for everybody, a win for the public health, for the clinicians, and get patients and physicians to feel like they are contributing in a significant way that not only is

for the greater good, but that helps them or that they see a benefit to themselves?

DR. GREENE: Thank you.

I think actually we're going to break for lunch in just a moment. There are just a couple of announcements before we break.

DR. TITUS: If there is anyone interested in speaking this afternoon during the open public hearing time, please see me at this time.

Lunch for the committee. There are rooms reserved for you in the restaurant.

DR. GREENE: We will reconvene at 1 o'clock.

(Whereupon, at 11:57 a.m., the subcommittee was recessed, to reconvene at 1:00 p.m., this same day.)

AFTERNOON SESSION

(1:10 p.m.)

DR. GREENE: If we could come back to order, please. We're coming down the home stretch. It has been a long day and a half.

First of all, although we're scheduled to have the whole afternoon available for discussion, for people who have to catch airplanes and whatnot, it's hard for me to imagine that this is going to go to 5 o'clock starting at this point. We'll see how the discussion goes, but it's hard to imagine that this is going to go till 5 o'clock.

I'd like to start the afternoon by giving Dr. Andrews an opportunity to speak for a minute about an issue that she raised with respect to differences in the way registries function. So, go ahead, Dr. Andrews, please.

DR. ANDREWS: Great. Thanks a lot.

Evelyn and I had been speaking earlier, and we were talking about the different approaches that have been taken in the registries, and I thought it might be worth a little bit of discussion in the group.

We heard from Holli this morning about the adverse experience reporting system in which adverse events that have been in some way associated with a medicine or reported to this AERS system, which is a numerator system, which has been useful at times in raising new signals

because rare events that could never be detected by the best epidemiologic studies will often come to attention of that system.

We also heard that it really is not a system for common events that can be measured in other ways, and that the FDA is considering in its new guidance, how it's going to guide those of us who do registries regarding reporting of events. In one model every event that comes to the attention of a registry would need to be reported on the MedWatch form and then tracked and followed up, and through a mechanism, if these are considered to be studies, then what becomes reportable is an association. And an association in an epidemiologic study is made not by the review of individual cases but by the aggregate data and the analyses. So, what's reportable then would be the finding or individual cases that have been associated or attributed.

I think it's important for us to acknowledge the issue of practicality and I keep coming back to that. If we were to register 1,000 exposed pregnancies and every adverse experience under the surveillance database system were to be reported, that would be 30 birth defects, maybe 150 spontaneous abortions, and 300 elective terminations, all of which would need to be reported by the registry to the company, from the company to the FDA, tracked in annual

reports. The amount of work in doing that is not trivial, and the amount that's learned from that information is certainly something that would need to be considered if we're talking about using that system in addition to an epidemiologic evaluation of the safety data.

So, I wondered if there were some other comments about that from people who have been working with registries.

DR. HOLMES: I have a request of the FDA on that point. If there were very clear descriptions of what needs to be reported on the MedWatch, it would save an enormous amount of time because whatever number you use for major malformations, it's only 2 percent or 3 percent, whatever number you use. But half of all newborns have a birthmark. 40 percent have one minor anomaly. The frequency of normal variations is up there; deformations, Lord knows. So, it's very difficult for a company to say be sensible because they're afraid they're going to get criticized for not being complete, but if you're complete, you're generating so much personnel time and what you get on the other end is not really penetrating information. So, it would really be helpful if it were in print so we could hold it up and say, now, look, this really doesn't fit what the FDA is expecting you to report.

DR. JONES: But, Lew, is it reasonable anyway

to think that a registry study that is set up the way we've been hearing the registry studies are set up -- is it reasonable to think that minor malformations in development are going to be picked up on the physical examination anyway unless you're doing a very careful physical examination to document those things? Certainly we've heard that that's not occurring and certainly we've heard that all that's being looked for are major malformations in development.

DR. HOLMES: Oh, yes. No, the problem is if you contacted the pediatrician, the pediatrician will often just photocopy the newborn exam form and send it to you. Now, the logical way to do this is to say, we're focusing on major malformations, those are what we will send. We've established our criteria. That's all set.

The problem is if you ask someone at a company, well, gee, the pediatrician noticed a birthmark on the back of the neck, the stork bite, well, most of the people at the company say, I can't say don't send that in. And yet it doesn't make any sense to send it in. And the problem is there's nothing in writing that you can go to as the basis for being sensible.

DR. SHARRAR: It is a difficult situation because we do try to follow the FDA regulations. The only reports that are sent in within 15 days are the serious,

unexpected reports, and the serious definition is the FDA definition which does require something like hospitalization or major disability or life-threatening. So, a lot of the minor AEs we learn about are entered into the database and reported on a periodic basis. All of the spontaneous abortions, all the elective abortions are considered serious and they are reported to the FDA within that time frame. It does take a lot of effort to do that.

DR. GREENE: Jan?

DR. FRIEDMAN: I think one possible solution to this is to look at a system where the norm for birth defects and other pregnancy related problems is not this spontaneous reporting system but rather a centralized registry system. So, if the norm were a centralized registry system and there were periodic review of all the birth defects that came in through that system, then the reporting requirements could be geared to that reality rather than having a hybrid system where you're trying to put reporting requirements on a registry where they really don't make sense.

So, it seems to me that if we stepped to the point and said, all right, the norm now is a central registry system, it has to have review of all the cases by an expert panel and there has to be reporting to the FDA every 3 months or 6 months of whatever is going on in that

registry, then it might be possible to avoid these problems.

The real problem with the spontaneous reporting is not the signal; it's the noise. I mean, there's just a tremendous amount of noise.

DR. GREENE: Other comments.

One thing I was thinking about as I was thinking about who was around the table here, I was trying to think of who might not be represented. It occurred to me that one group that might not be represented is sort of rank and file working docs, including obstetricians and pediatricians. I think that one of the reasons that the registries, such as the Varivax registry has worked where physicians responsible for reporting prospectively exposures, is because there are relatively few such registries. I could envision a situation where there was a registry for virtually everything which required physicians to report in outcomes at the ends of pregnancies that would be incredibly burdensome to physicians. In view of the fact that even if you take away relatively trivial exposures, multiple vitamins and hematinics, nonetheless, you have a very substantial fraction of all pregnant women who are exposed to some sort of a medication during their pregnancy. That could be a tremendous burden upon practicing physicians and I would question the value,

validity, and completeness of the information that would result from such an extensive requirement for reporting.

DR. MONTELLA: Mike, I might be able to comment some on that because of a couple things I do. One is as President of the Society of Obstetric Medicine, we're working with both the Australian obstetric medicine site and the McDonald Club in England, which were all the obstetric medicine people, and this is all of the internal medicine people, including rank and file internal medicine people, who are exposed at all to medical complications of pregnancy.

Then additionally, the ACP, the American College of Physicians is a huge group of rank and file pregnant care docs out there who we do all the teaching of the medical problems in pregnancy for the ACP. The people in those workshops are clamoring. So, I see probably like 300 to 500 people each year that are asking questions about how do I take care of pregnant patients with medical problems. And they are clamoring for registries. They're actually asking is there a place that we could go to bring this information, is there a place where we can get more of this information. So, somehow if we disseminated this properly, my guess is it would be an appealing thing. Now, you can probably speak more to the obstetricians' view of that, but I can tell you from the people administering the

drugs for medical things, that I'm hearing a request for it, if anything.

DR. GREENE: Well, for internists, the number of pregnant patients in their practice is a relatively small fraction, whereas for an obstetrician, the number of pregnant patients who are taking medications is a very large fraction.

Don?

DR. MATTISON: Two other potential approaches that get to that. One would be to get your group together with NICHD's maternal-fetal medicine network. Jim, I don't know if you wanted to comment on that as a potential study group. Certainly that could be expanded nicely, as far as I could tell.

The other relates to managed care organizations and the way that both administrative and clinical data are kept in a managed care environment and the potential for that to provide information that gets at some of the same questions.

DR. GREENE: My only first thought is that if you look at the demographics of the patients that participate in the maternal-fetal unit network studies, they don't look anything like the demographics of the United States of America.

Other comments? Ken?

DR. JONES: This gets back to what you said about the success of Merck's study that we heard about this morning. I guess I would like to ask a question. Has that registry in fact been successful? And maybe that's not a fair question, but I would like to try to get at that issue. It seems to me that it has been very successful in terms of showing that there does not seem to be an increased risk for the full-blown fetal varicella syndrome in babies born to women that get this.

On the other hand, there are a lot of babies who are exposed to varicella whose mothers have varicella, who do not have the full-blown fetal varicella syndrome but have subtle features of the fetal varicella syndrome that clearly show that that child has gotten the virus that I would suggest that perhaps you would not have picked up in the study the way the study was designed.

So, I'm not sure that, in fact, this study has been successful in terms of answering the question that you think it has. I mean, it clearly has answered the question this is not associated with that baby who has horrible skin defects and contractures and hydrocephalus, not at all. But there are clearly a lot of features of the fetal varicella syndrome. It's a spectrum. It's a wide spectrum. I don't think that you really have answered the question as to whether those babies have an increased risk

of that.

DR. GREENE: So, the question that your question asks is, how do you know if you've been successful?

DR. JONES: Well, I would question whether the study has been successful. I, to be perfectly honest with you, would suggest that it has not.

DR. GREENE: Dr. Sharrar?

DR. SHARRAR: Well, it depends upon how you define successful. I think you have to realize that we are dealing with post-marketing surveillance data, so there's not a doubt in my mind that we have had incomplete reporting.

We also have so far dealt with the obstetricians and with the consent form. We're trying now to get now more follow-up information up to the second year of life. Plus, if you take a look at the data, although we have over 400 people in the registry, we probably only have something like 80 individuals who are truly identified as being seronegative before they got the vaccine. So, these are other issues that we are taking into consideration.

We will not pick up the subtle defects. I'm not sure it's possible to pick up the subtle defects, particularly if they're rare. I think we will continue the registry for a number of years until we get enough women

who were susceptible when they got the immunization, when the immunization was given during the crucial time period of pregnancy, which happens to be the second trimester, not the first trimester. After we have enough of those individuals, we'll at least be able to address the question of significant malformations. I'm not sure it's possible to address the subtle changes because I don't think any epidemiologic system is designed to do that.

DR. JONES: Well, that really is not true. The birth prevalence of the fetal varicella syndrome has been documented through prospective cohort studies. The 1 to 2 percent prevalence of the fetal varicella syndrome has been documented doing relatively small studies of 100 to 150 women who have had varicella themselves and then looked at their babies through -- two of the studies were done by teratogen information services and one looked at 158 women and the other I think about 110 women. And all the babies were examined, and by virtue of that examination of that prospectively ascertained case, one was able to pick up not only the children who had the full-blown syndrome but children who had much more subtle abnormalities as well.

So, I think that with an epidemiologic study this definitely can be done, but I don't think that the type of study that you have done -- and believe me, I'm not being critical of you for the study. I think it's

fantastic that you've done these studies, and I think it's certainly to be encouraged to do these studies. But I don't think it has been successful in answering the question is the vaccine associated with the fetal varicella syndrome because you have to examine the kids in order to do that, and you can examine the kids.

DR. GREENE: Well, I guess the question I would ask, Ken, is how important is it to document those very minor problems?

DR. JONES: It's particularly important to document those very minor problems when they're an indication of a defect in brain development.

DR. GREENE: If they are.

DR. JONES: If they are. There are children with the full-blown fetal varicella syndrome who have been tested and are normal from the standpoint of their intellectual performance at 4 to 7 years of age, and there are likewise children who have the full-blown fetal varicella syndrome who are devastated from a neurologic standpoint. And also, there are children who have only the minor features of the fetal varicella syndrome who also have severe problems in intellectual performance.

So, I think without any question, it's important to document. I'm not talking about syndactyly between the toes. I'm talking about subtle indications of

neurologic abnormalities like a problem with like a cataract, for example, or with pox marks on their forehead or with a Horner's syndrome or something such as this that's more subtle that can be an indication of a problem in brain development. So, I think it is critical to examine those kids.

DR. GREENE: Jan?

DR. FRIEDMAN: I agree, and this is an issue that I raised yesterday with respect to the acyclovir registry. It seems to me that it's not enough to know that we're not dealing with a thalidomide or an isotretinoin in a registry. There's enough power there, if you look at the kids right, to also say we're not dealing with a fetal alcohol syndrome, and I think we should know that there's not a 10 or 20 percent chance of something like the fetal alcohol syndrome. And you're not going to get that unless you look at the kids. I think that's really what has to be done.

DR. HOLMES: Mike, one model that we've talked about for the antiepileptic drug registry is to say, all right, you've got the registry for the big outcomes of concern, like the major malformations. If in your consent form you're given permission to recontact the mother later, then let's say you identify drug X where you're worried about a half a standard deviation effect on IQ, you could

then organize a particular focused study of that subset to take on that issue or, if it were the one that Ken is talking about for varicella, something like that. But have the registry for one purpose and that is a potential source of individuals for additional things. Certainly when the biomarkers come along, that will be an important subset to go after. But it fits within the idea of a registry in general with foci as they seem necessary.

DR. GREENE: Allen?

DR. MITCHELL: Yes, but that's speaking to the issue of power and I think it's a good mechanism, but it doesn't deal with the issue of confounding. It doesn't deal with the issue of bias. I share your concern, Jan, but if you're worried about a fetal alcohol syndrome in a cohort of kids exposed to a drug, but you're not asking about alcohol exposure in pregnancy, it's pretty hard to do.

My fear is that we're again back in that sort of spiral of demanding of registries that they have to be able to ultimately answer every question, and I think they need to be viewed in a very limited way. I think, Ken, you're asking a legitimate question about the minor abnormalities that may or may not reflect some intellectual deficits, but I'm not sure that's within the normal, typical registry to answer. Again, it becomes an issue of

one size doesn't fit all. If that's the objective, you have to design a very different study.

And I think the worst thing to do is to propose that we're going to be looking at, quote, a fetal alcohol syndrome as a result of drug X without even knowing about confounding variables.

So, it really is incumbent on the community -- we keep coming back to this: Well, what's the registry all about? I think in different drugs it will be different questions.

DR. FRIEDMAN: But if you're only looking at, say, 100 kids and you're actually looking at them, you have a physician who's seeing the kids, it's possible to ask those questions in a nonthreatening way. You don't have to ask them on the phone to someone you've never met, you don't know anything about. It can be asked in a clinical context. You can see that it's not fetal alcohol syndrome that this kid has but minor manifestations of a varicella embryopathy.

I think this is going to require collaboration between physicians, between clinicians, and epidemiologists. There does need to be epidemiological rigor, but there also needs to be clinical rigor.

DR. MITCHELL: But, Jan, are there resources in the world sufficient to do that for every exposure that's

going to fall into a registry? I don't think anybody would disagree on first principles that there ought to be a standardized clinical exam, but are there going to be resources? This is the tradeoff. Where do you put the dollars?

DR. FRIEDMAN: Well, it seems to me that there are resources to ask whether or not a mouse has birth defects because of a drug and a rabbit has birth defects because of a drug. It seems to me it's not unreasonable to ask if people have birth defects because of a drug.

DR. MITCHELL: Well, but let's be serious and talk about a finite amount of resource.

DR. FRIEDMAN: I'm not saying 10,000 kids. I'm saying if you want to pick up a thalidomide, we said you need 100 kids. If you want to pick up a fetal alcohol syndrome, maybe you could do it with a similar number of kids if you actually looked at them.

DR. MITCHELL: But if you want to pick up a thalidomide, you don't need to have a directed, specified clinical exam.

DR. FRIEDMAN: That's right.

DR. MITCHELL: And the costs of doing that are huge. The benefits are huge too. I'm not against it. All I'm saying is that there are going to be societal decisions that have to be made about where do we invest our dollars,

and that's a tough call.

DR. MITCHELL: Sure.

DR. GREENE: Yes.

DR. WEISS: I think it's one thing to ask a question when the animal studies are positive and you have a directed hypothesis to put the resources into that kind of analysis, but when you have like a new molecular entity that you just want to know is this something that we have to worry about, let's just screen it, I think it's a whole different study design, more toward the registry that we're talking about as opposed to a well-controlled longitudinal cohort study that you want to do. I think you really have to ask what your question is and let your design follow that and think about the public health implications before you put a lot of resources into the question.

DR. GREENE: Don.

DR. MATTISON: Maybe this is a good time to follow this discussion with one of the questions that I raised earlier because the extent of interest in reducing uncertainty around the potential for development toxicity in part can reflect the potential benefit that the pharmaceutical company derives from reducing that uncertainty.

So, what are the potential benefits? How can regulations be structured or the environment be structured

in such a way that there are actual benefits to the pharmaceutical industry for understanding pharmacokinetics and pharmacodynamics in pregnancy and for conducting or supporting studies which reduce our uncertainty about counseling for developmental toxicity? And how should the agency think about that, or how should Congress think about that?

DR. GREENE: And how would the manufacturers? What would they view as adequate incentive to do that?

DR. SHARRAR: That's a difficult question to answer I can tell you that. I do think the pharmaceutical companies try to address the significant safety issues that are of concern to us. To try to look for a very remote safety issue is probably not something they're going to want to invest their resources in. I cannot speak for the entire pharmaceutical company, but we do the best we can with the limitations we have.

One of my concerns about the study you're proposing again goes back to the very foundation of what our study is. It's an observational, epidemiologic study based upon limited post-marketing surveillance data. I would not use that kind of data to try to do the kind of study you're describing looking at very subtle behavioral developmental changes in individuals without having a great deal more knowledge on the environment that they live in,

their parental heritage, a lot of other exposures that occur during pregnancy. And we're not prepared to enter into that kind of a study.

DR. ANDREWS: I think that pharmaceutical companies are increasingly responsive to what consumers want and need, and this is an area of great need. It's been very difficult in the past to find a way of communicating information about safety as opposed to risk, and as we've heard before today, the entire system for pharmacovigilance really is one that has been aimed at finding new signals of problems, not documenting any level of safety.

So, I think sort of a paradigm shift or some way of facilitating the communication of information that can be viewed as reassuring with all the caveats is of tremendous benefit to patients and practicing physicians. So, some better way of communicating the information that can be gleaned from these studies would be an incentive.

DR. GREENE: Sandy?

DR. KWEDER: Elizabeth, can you be a little more specific on what you mean by ways of communicating information?

DR. ANDREWS: As we were talking about earlier, putting information in the label, for example, which is our fundamental document that we speak from, finding the right

way of stating the evidence so that we certainly don't overstate it, but being able to have some data that in fact are more reassuring than no data or what consumers may have heard or think from other sources I think would be tremendously helpful.

DR. GREENE: There's an issue that you brought up earlier in the meeting, Sandra, that I'd like to get back to, and it fits with this nicely, and that is differences in perceptions of risk when presented with the data. Those of us who are in clinical medicine are very familiar with the idea that we'll see two different couples. We'll counsel them about the risk of having a miscarriage from doing an amniocentesis and we'll say it's 1 in 200, and one couple will see that risk as trivial and another couple will see that risk as very imposing. The numbers are the numbers and how people perceive them is different from couple to couple.

I think that when communicating risk, we have to be as honest and as quantitative as we possibly can, recognizing that different people are going to see the numbers differently. I don't know how better to do it.

Jim?

DR. LEMONS: I thought that discussion, Ken, that you presented on the Varivax is a very clear example of how that -- you have a very specific constellation that

you're looking at. You know it may be related to neurodevelopmental delays. It can't be accomplished by industry given the resources and limitations. It requires a very different study design. But that's where you have a clear, almost hypothesis. For the vast majority of medications, we don't. And then you look at syndactyly. Is that important? Probably not.

But I guess to get back to what Don raised earlier, to ask those specific hypothesis-driven questions probably requires a different infrastructure. There are a lot of infrastructures around such as the Maternal-Fetal Medicine Network I think. Even though they don't represent demographically the typical constituency of the United States, they still house a huge population of -- I don't know -- 75,000 to 100,000 in-born post-referrals that could in very powerful settings of academic, pediatric, and obstetric communities address these questions where you may need 150 cases of maternal exposure. So, it gets back to what you had suggested, Jan, of kind of a housing of a variety of powered infrastructures to address specific ranges of questions.

DR. GREENE: Ken?

DR. JONES: It seems to me that it points out the need for doing a variety of different approaches to look at the same problem. For example, it seems to me that

a study, an industry-driven study, in which you looked at 1,000 children in the way you have looked at 1,000 children, and then one took a subset of those children and looked at them the way we look at children, which is to do a very careful physical examination on the children -- we certainly can't do that careful physical examination on 1,000 kids, but there are questions that can be answered, it seems to me through both approaches.

It seems to me that we've got to recognize -- and I think people have been saying that, but I think this is another example of reasons that we have to look at different strategies and different approaches. And they're all represented around this table. There's no one way to look at this. We've got to look at it in a variety of different ways to answer different questions.

DR. MILLS: I was just sitting here making a list and looking at the question of how are we going to decide where we're going with this in terms of what's doable financially, how would we design a study. Many people have already touched on the question, well, what are some of the different things that we might be doing?

Without spending very much time on it, I came up with two major categories and a number of subcategories. If you started with all drugs as you're target, category A, you could have A1, which is to look for thalidomide, which

means you need maybe 10 or 100 people to see if there is a catastrophe going on there. You would have A2, which would be to look for birth defects in general without any particular focus where you would need maybe 1,000 or 10,000 people. You would have A3, looking for a specific birth defect maybe based on animal data or on related information from other drugs, where you might need X thousands or X tens of thousands of people.

Then there's approach B where you look only at selected drugs, the sort of hot drug approach. And B1 you would look maybe for a sentinel defect, for example, with something like fetal varicella where you had a pretty fair idea of what the natural situation was and you might argue that you'd want to focus on that. Then you'd have B2 which is where you would want to do an A to Z evaluation, for example, if you thought it was a vitamin A story where you wanted to look at cranial neural crest defects and you knew that you had a wide range of defects that would require some fairly sophisticated evaluation to pick up.

The reason for going through this exercise is to point out that the population varies tremendously from maybe going to one clinic to going through a wide swath of births coming from a large underlying population. The cost varies tremendously depending on whether you're going with telephone self-reports to having to track down individual

exposed children and do an examination. Of course, most of all, the kind of follow-up varies, going again from self-reports to a very sophisticated exam that might only be doable by fairly specialized people.

So, the point of this is to say that when you're talking in the abstract, it's going to be very difficult to determine whether these are feasible, how we would approach it, and which direction to go in because we're talking about just completely different areas and different needs. I think we have to recognize that some of these things are doable, some aren't. Some are to be approached one way and some have to be approached a different way. It's not an easy thing. Maybe we need a workshop just to get into that issue.

DR. MATTISON: There's another component and I'll bring up the obscene phrase that I used before, which is biological plausibility. Even new chemical entities, those that have not been used in the development of a clinical product before, hit the market with a substantial amount of understanding within the pharmaceutical company that's developing that chemical entity about how it works and about what it doesn't do. We're talking about the design of post-marketing studies as if an understanding of the biological mechanism was pretty limited. Whereas, I think actually we should be asking within the company

what's known about things that these molecular entities do and don't do.

Companies invest a huge amount of money in getting a product to this point, and they want to know does it bind progesterone receptors, does it interact with a range of other factors, what happens to immune function, what happens to really very specific kinds of targets across a broad range of biological systems. And they do that because they understand that you can extrapolate from cell culture to intact animals to humans. How does that information get built into helping us understand?

For example, if we knew that a particular molecular entity blocked cell motility or impaired cell motility, there's a set of hypotheses that would be derived that could come from embryonic studies, and in fact maybe you wouldn't want to go any further. But if you did, you would have some understanding of how to look for potentially endpoints in biological systems. So, there has got to be some way of getting this broader and richer array of data back into the equation which allows us to reduce uncertainty and then build these population based studies in a much more meaningful way.

DR. GREENE: I'd like to turn now to addressing the specific questions that are in our agenda packet for this afternoon's discussion, and that is to start with very

specifically a discussion of a centralized registry. The first bulleted question that we're asked is, how could a centralized model help to overcome existing obstacles and what additional problems or obstacles might be introduced in a centralized registry. The whole idea, of course, is broached by the last item in your agenda packet, which is the proposal for a centralized registry conference to discuss the idea. Please.

DR. WISNER: I'd like to start with a very provocative statement that was on one of the slides this morning which was that a pregnancy registry had never identified a human teratogen. I think in terms of identifying obstacles, we would have to be certain that whatever registry we agreed to formulate, it would be able to overcome the obstacles that have created the situation designated on that slide. I'm not sure what those obstacles are that have created this issue of no human teratogens being identified by registries in the past.

DR. MITCHELL: I want to disagree with you. I think that that's one interpretation of that statement, but I think the other interpretation could easily be that the registries that have so-called failed to find a teratogen have not found one because it doesn't exist.

I think the point is that we want to provide information and that information may be negative in the

sense that there's no adverse outcomes or it may be positive in the sense that there are adverse outcomes. But I think the vast majority of drugs that we use are probably not teratogenic and we shouldn't begin with the assumption that they are and our job is to find it. So, I think that if there is that perception, then we really need to educate people about the mission and the reality of registries.

DR. WISNER: Let me follow that with probably what is a nasty situation, but I think it's relevant to your point which is the lithium registry which in fact did identify a teratogen, although because of the problems in the way the registry was done, it identified it to a degree that probably was destructive in the sense of believing that affected pregnancies would be highly at risk for an abnormal outcome. So, at least that registry had identified a teratogen.

I guess my question was really related to what you said in the sense that we have to identify why, other than lithium, registries haven't identified the human teratogens. One may be what you say that, in fact, many drugs aren't teratogenic, but it may also be then that setting a wide net and looking at all new agents may be futile and expensive. Then the question becomes how do you narrow the selection of agents down to the point where it's more cost effective. So, it's more identifying those

things that I was thinking of.

DR. MITCHELL: I agree with you. I think a recurring theme is the notion of not only targeting study designs but also targeting the drugs of interest. The lithium registry is a very good example of study results being misconstrued, but that the basic design was not necessarily flawed. The same argument can be made about any other prospective registry. It can be made about any case-control study. So, I think again we need to separate interpretive issues and design issues from the concept and what these systems can contribute.

DR. GREENE: I think the lithium registry is also a good example of what I was saying yesterday of experience is great because it helps us to recognize our mistakes when we make them again. If you, early on, identify something that you think may be associated with an exposure, that begets reports of other similar problems to the exclusion of the negative reports or the exclusion of other kinds of problems.

DR. MITCHELL: Actually if I can take that example to the extreme. Some years ago -- I'm sure many people on this panel will remember -- there was concern about caffeine being a teratogen. A consumer group set up a registry where consumers were encouraged to report birth defects that occurred to them if they had been drinking

coffee, and guess what? There were a number of reports that came in. So, that's the extreme.

But in fairness I don't think anyone is suggesting that kind of design. So, we need to use those words carefully. We're not talking about a retrospective registry, and here I'm using "retrospective" pejoratively.

(Laughter.)

DR. GREENE: Getting back to the centralized registry versus disseminated registries, Jan, did you want to speak to that?

DR. FRIEDMAN: Well, I wanted to speak to the issue of why there haven't been many signals from the registries. I think there are two important reasons. One is that we do have preclinical studies and I think they do do something. I think they do detect some of the thalidomides and they never make it to market.

A second reason is that the registries we have -- we have said it over and over again -- don't detect subtle teratogens. They don't detect things that increase the risk of cleft palate twofold or produce a subtle pattern of dysmorphology that doesn't get reported on a one-page form. All we can pick up is thalidomides and there aren't very many thalidomides. Thank goodness.

DR. GREENE: Okay. I'm still looking for someone to speak to the issue of centralized versus non-

centralized registries, please.

(Laughter.)

DR. GREENE: Yes.

DR. WEISS: I will, kind of. One of the things I see as a problem with centralized registries is that they don't allow, necessarily, the flexibility to use the a priori hypotheses and information to design something that might be able to pick up something that you might suspect. So, that's something that I am concerned with.

DR. GREENE: Why not? Why wouldn't they?

DR. WEISS: Because if you're doing a standardized protocol, there may not be the flexibility to design a study in such a way that you would -- for example, what you were saying, Dr. Jones, about going and doing examinations if you had a hypothesis. I mean, the registry wouldn't be the right model necessarily to look at that. But if that's kind of the standard, that might be what you'd go to first just because it was the standard.

DR. GREENE: But just to continue the discussion, if the registry were, if you will, the hypothesis generator, then the specific studies could be layered on on that.

DR. WEISS: I was kind of going with the hypothesis generator might be the animal data and that you would want to go right into that.

DR. MITCHELL: Yes, but even so, we don't need to think of the registry as a monolithic design. I could easily envision a registry where for drug A these are the outcomes you pursue. For drug B, you might have the Ken Joneses of the world be examining a subset. I think that by centralizing the activity, my sense is that the major advantage you offer is simplicity on the part of the public and the physician community in terms of identifying potential subjects. Once in house, the registry can allocate people to different designs.

DR. WEISS: I feel like the word police today.

(Laughter.)

DR. MITCHELL: Point taken.

DR. WEISS: What I'm thinking of maybe then isn't a centralized registry and maybe you kind of said that. I'm thinking of more a centralized clearing house might be better thing where there's a clearing house that helps advertise, enroll. It would be able to bring data forward from different studies so that you'd have comparable baseline rates, that you might be able to use also a source of expertise and resources for the design of different registry studies, help with recruitment and then interpretation. Now, that kind of centralized resource I think is incredibly valuable.

DR. MITCHELL: Well, I think if the Pregnancy

Labeling Committee does its work well, then we're going to have these letters left over, A, B, C, X, that weren't used.

(Laughter.)

DR. MITCHELL: So, Jim has coopted a couple of them, and it seems to me that there's no reason that registry couldn't have plan A, plan B built into its design. I think it could be more than a clearing house.

DR. WISNER: Just to follow up on what Jan said, I think a centralized registry could really expedite getting those 100 cases to see if a newly released drug is a thalidomide or an Accutane or whatever. It could get that information together quickly rather than waiting for those cases to accrue after the drug is released.

But I have a harder time seeing how a registry might used for the most specific kinds of studies that Ken talks about because you have the centralized registry. They might be able to identify, say, cases in a particular city or region that might be accessible to the pediatric exams or the longer-term follow-up, but in some ways having it centrally, other than a case identification, is a disadvantage for those studies in which the cases actually need to be physically examined.

DR. GREENE: Yes, please.

MS. CHAMBERS: We sort of do that now. We have

two nationwide sort of registry type projects that are running that have two different study designs that are run out of a central location. So, one is looking at pregnancy outcome in about 1,800 women exposed to asthma medications looking at only at major malformations and complications of pregnancy and in the newborn only by own physician report with no physical exam. Allen brought up the point about use of resources. The cost of doing that is approximately equivalent to the cost of seeing 100 kids doing a careful physical exam. So, the tradeoff I think is about equal.

Then the other study that we run out of the same central location is this Arava study, which is looking at a far smaller number of kids, 300, 100 Arava exposed and two control groups, and those kids, the live-borns, are going to get physical exams throughout the country. So, there are four dysmorphologists that will see them in the locations where they're at.

So, it's feasible I think to do it from one central location. There's a lot of efficiencies involved in it, having personnel that cross over into both projects, and as we add more projects to it, if we do that, if the group decides that they want to do it, I think it becomes more efficient, more standardized and yet it's not the same protocol for each one. There are different questions. There's a severity assessment that's administered with the

Arava project and a different one with the asthma project.

As Don brought up, based on the animal studies, that drove the specific reason that we set up the Arava project the way that it is because there was enough concern about this drug in pre-marketing animal studies to suggest that it should be looked at with this level of scrutiny, whereas with asthma medications, we're talking about a number of drugs that we have a long history with, and the issue is major malformations or has been in the past. So, I think it's feasible.

DR. GREENE: Dr. Kweder.

DR. KWEDER: I just had question for Christina. What's the budget for each of those two studies, just roughly?

MS. CHAMBERS: We do everything on a shoestring. You should tell me if this is correct or not, but I'm going to say a four-year study for about $300,000. Is that right?

DR. JONES: $500,000.

MS. CHAMBERS: $500,000.

DR. GREENE: I would like to hear actually some comments from industry representatives as to whether they would welcome the idea of a centralized registry as getting them sort of out from the middle, if you will, or absolving them from being in the position of appearing to be the fox

watching the henhouse or whether they would find the lack of control of budget, et cetera, et cetera, as being anathema.

DR. SHARRAR: I'll try to address some of those questions, and then I have another question for you.

I think the pharmaceutical company, as I said earlier, is interested in describing the safety profile of our products. We're not interested in turning it over to someone else to do. It's almost like when you have a child and you're raising it, you don't give it to someone else to raise. We have a proprietary interest in our product. We want to make it as safe as we can and we want to make certain we understand exactly what it can and what it cannot do. So, I can speak for Merck. We're not really interested in turning over the registry.

That doesn't mean you can't have a centralized registry. I think the important thing is that we share and cooperate with each other as we analyze the data because no one individual has all the correct answers.

I'm a little confused on what we mean by a centralized pregnancy registry because when I first thought of it, I thought of a centralized registry as a registry like the HIV pregnancy registry. It's disease oriented. We're collecting information on people who have the same disease but who are receiving different drugs. That kind

of make sense because there's a lot of interaction between the two.

I never thought of having a varicella vaccine pregnancy registry as a central registry because we're the only one that manufactures the drug, and it's not a drug that you routinely use in pregnancy and it's not a drug you have to use in pregnancy. So, I don't really see any need for a centralized registry for that.

I'm hearing that we're going to have a centralized registry for all drugs on the market, and that's really a big undertaking that I won't even begin to know how to do because we're interested in our products. I don't really know or understand all the other drugs out there that are manufactured by other companies. Maybe that is the correct way to go, but right now I'm not willing to make an investment in a centralized registry that contains a lot of drugs that I know nothing about and are not part of our company's interest.

DR. GREENE: Well, I think that this is a good opportunity then to ask the people from the CDC and the FDA who have been sort of germinating the idea to be more precise about what they mean.

DR. CRAGAN: I'm not sure that we're precise about what we mean. I think it could go in several directions. We don't necessarily mean that a centralized

registry or a central plan for these kind of studies is going to displace or override the studies that are in the registries that are out there. I don't think that's anyone's intention. If there's the interest in folding some of those activities into a more centralized thing that's administered differently, that could happen.

We're really talking about the future and the long-term future of how to do this. My guess is that the way people perceive that is going to vary from company to company. Some of the smaller companies that don't have the resources to mount their own registries but would be interested in having some of this information on their drugs perhaps would be willing to help with the centralized approach.

Elizabeth, do you want to add?

DR. ANDREWS: I was going to answer the questions on the industry perspective. You said does this get us off the hook. Nothing gets us off the hook from owning the safety agenda for all of our products. Nothing will ever get us off the hook.

There is a concern about lack of control of information because in an academic center where you're looking at the theoretical risks of different drugs compared to each other, it might be easy for someone else to say we don't yet have a statistically significant

finding. But we're less inclined to wait for statistical significance when there's a signal of an issue. Then we'd like to be involved in in exploring that, as Don was saying, looking for the relevant information from other sources, testing a hypothesis in another model. So, I see this as a very interactive process as the data evolve, and it makes me less comfortable to see a centralized registry in the sense of a vanilla, one-size-fits-all, and I don't think that's what's intended at all.

What is appealing is some easier mechanism for enrolling and communicating with the physicians and patients so we're not creating confusion for them. I think the centralized antiretroviral registry and the antiepileptic drug registry are very good models for collaboration in disease areas where we really need to know more comparative information about different drugs because women really need to have that information.

DR. GREENE: And I think the advantage of the antiretroviral or the antiepileptic drug registries is that if you ask the average doc on the street who is prescribing either an antiepileptic or an antiretroviral which drug company do you call to report a problem with this drug, they probably don't even know who the manufacturer is of that drug. It's not on the tip of their tongue. That's not what they pay attention to. So, I think that's an

advantage of either a group of pharmaceuticals or a disease-oriented kind of a centralized reporting system.

DR. ANDREWS: Can I just mention that one of the best ways of getting reports is from people who are calling with a question. People call pharmaceutical companies for questions about the safety of their drug in pregnancy, and that's one of the largest sources of referrals to these registries.

MS. CONOVER: Actually, just to open that hornets' nest, I was thinking of that too. When I call, I'm always looking for information, and I don't mind reporting my case in to add to it. But there's a real question for me about who would have access. Would you be giving information back? Say, if you have patients calling in, would you give them what's already in the database in trade for them submitting their case? The same thing with physicians and who would be the qualified person to do that or to start to control where that data goes and who has access to it?

DR. GREENE: Pat?

DR. WIER: Yes, Mike, I want to come back to the initial question about the concern for potential bias of a sponsor running a registry. But the flip side of that coin is accountability, and Dr. Sharrar has done a good job of enunciating the sense of product stewardship that

companies carry forward.

But to put some real flesh on that, this accountability can be very focused. There are penalties that can be extracted if data is not forthcoming, if data is not interpreted correctly. The agency knows where to go if these problems exist. So, I would turn this around and say in the concept of a centralized registry, where do you go for that accountability? If you have a centralized registry tracking 100 compounds and some data is late, it's not being taken care of properly, who is accountable? You could be in a bureaucracy where you would run from one person to the next saying, well, that's not my responsibility, I deal with this compound. So, I think that's the other side of the argument that needs to be presented as well.

DR. GREENE: I think, Sandra, you can take that down as an answer to would additional obstacles be introduced.

DR. KWEDER: I think those clearly are issues that do need to be discussed. I just wanted to weigh in because you had asked for the FDA and CDC to articulate a little bit better.

One of the reasons that we even began this process to explore registries is because what we see is we see the Mercks and the Glaxos who are interested in this

and take their responsibility to collect this kind of data in this population in a carefully designed way very seriously and have the resources to do it. We see the full breadth of the spectrum, though, and I would suggest that the vast majority of companies don't have the resources, just the knowledge or other resources, to collect these kind of data.

That's part of our interest in finding ways to facilitate the collection of more and better data so that 10 years from now we don't still only have information from large data collection efforts on 15 drugs and it's only up to 20 now, that there's more data on a broader array of products, some of which are likely to be used a lot, some of which may only be used a little but about which there are worries.

DR. GREENE: Don?

DR. MATTISON: The discussion of the central registry reminds me a little bit about the National Toxicology Program. It's a program that helps us understand the toxicity on chemicals and drugs, but there's a nomination process. It's managed by the National Institute for Environmental Health Sciences, and there is a group of other federal participants in this. All of the products that are studied are nominated externally.

So, I guess one of the questions that some kind

of a central registry would have to raise is who nominates the products. Could a group of interested obstetricians nominate a product that was still under patent by a company and how would the company feel about having that product nominated for a generalized population based evaluation? Who covers the cost of such a study? How is the data linked to other biologically relevant data, and is the company willing to share it?

As it turns out, there have been drugs that have been studied by NTP, but as I understand it, it's generally those for which there was no existing patent protection and for which questions have arisen about safety, basically drugs that fall into the generic class. It may be that a centralized registry would only work for drugs that are manufactured by more than one producer because the sense that I've gotten from Patrick and Robert and Elizabeth is this strong sense of stewardship for the safety of drugs or pharmaceuticals for which they are the prime manufacturer, and like your own children, you'd hate to give up responsibility for them.

On the other hand, there may need to be a way of calling in a broader range of data that describes biological impact or biological effect. I guess we still haven't gotten to how that might be structured.

DR. GREENE: Jim, you had a comment?

DR. MILLS: What I was doing was sitting here thinking about the comments that some of these groups might want to make except that they might not feel entirely comfortable.

I'd start out with the FDA since I don't work for the FDA. I'm sure there are some people over there thinking, well, we're not overburdened with money and we're not overburdened with staff looking for things to do. How would we oversee this whole project and fund it or even fund a part of it based on the monies available? So, I think either the FDA or somebody would have to think about that.

Secondly, if I were the person presenting this to the drug company board of directors, I would expect to hear questions like, well, will we have no control over the course of these investigations, or will we have seats on the oversight group, and if so, how many? That's another question we're clearly going to have to look at.

If I were that same board, I'd be asking, well, how is the cost going to be divided among the companies for this central registry? Is this going to be the sort of thing where you kick in for each study that involves one of your drugs, or is this going to be co-funded as a larger "pass the hat" collection among the participating companies?

Also, I guess the most cynical question would be, well, what's the wisdom of having our drugs looked at all? There are some cases obviously like thalidomide where there was no way that that was going to be on the market without some pretty good monitoring, but for the average company and the average drug, they could make an argument that they participate in a registry, they look at 1,000 births, 20 of the kids had birth defects, everybody thinks that's fine, and some lawyer gets the data and says, ah, but 4 of those 20 kids had cleft palate or cleft lip and therefore there's a lawsuit here. So, they run a risk in that sense by participating unless there is some other compensatory gain for them looking at the drug that they may not have thought needed looking at in the first place.

DR. MONTELLA: I think the flip side of the stewardship of this information is the responsibility to release that information. So, if we're proposing looking at a series of drugs or a series of drugs in certain classes, you have to be able to decide which drugs. And in order to be able to decide which drugs, you need the information that Don has alluded to, you need the animal data that's been alluded to here. So, someone or some responsible advisory group needs to have that information to say which drugs, any drugs that there have been signals on.

If you look at even Gideon's article in the New England Journal, I was just remembering the table that's saying what was the animal data available and what was the human effect. If you look carefully at that table, we would have had some clues there about which drugs we might want to look at in that way. I think that we need to have that information to be able to use it responsibly.

DR. GREENE: One or two more and then I'd like to move on to the next. Dr. Wisner?

DR. WISNER: Let me describe a hypothetical plan and you can tell me whether this is feasible. One of the thoughts I was having, listening to the discussion, is whether it would be possible to have kind of a two-part system in which the first part is a drug is newly released, gets all of the typical designations that it does now, but a drug company would retain the responsibility for having a registry of sorts that would be standardized and that the first 100 exposures in pregnant patients would be followed by that particular drug company, at which point, if the data looked favorable by some definition, they could get yet a second designation that they had taken the responsibility for at least analyzing whether it was a thalidomide. Is something like that feasible?

DR. GREENE: Allen, did you have a comment that you wanted to make?

DR. MITCHELL: Yes. I'm sorry. I'm not responding to that. I'm responding to Jim's overly optimistic view of the world.

(Laughter.)

DR. MITCHELL: I think that in every example that you gave and every concern that you gave, I think there is a reasonable response, and I think given our own experience in doing lots of research sponsored by industry in negotiating hard contracts, first we've learned that industry is not monolithic in its views. There are many members of the pharmaceutical industry that for various reasons see distinct advantages in having academic groups working with them in their stewardship of their drugs. I think there are all sorts of creative ways to resolve a lot of problems.

Just as a case in point, when we began the Accutane survey, which incidentally was not an etiologically oriented activity, we were told we would never be able to enroll more than 10 percent of people who took the drug. Well, we came up with this idea of a direct enrollment form that was included in the medication package. That has never been done before. People thought it was ridiculous. Well, that accounts for virtually three-quarters of our enrollments.

So, I think that if we take a positive attitude

and we say that there are very few problems that are insurmountable, we have a chance at making things work. I recognize that there are a lot of problems, but if the objective is to develop information on more than a handful of drugs, then it's not a matter of whether the central registry is the way to go, it's whether the alternative is any better. If the alternative is disparate registries to which physicians and the public have to respond in disparate ways, I think that the balance is different.

So, if the objective is to get not information on every drug that's ever used, but more drugs than we have now, then the choice of the centralized registry, or in deference to Sheila's reasonable point, using the appropriate words, some centralized activity, I think really has some merit. And I'm willing to bet that if the industry went back and huddled on it and huddled with FDA and were given certain kinds of assurances that FDA might be able to give, that their attitude may very well be positive, including the largest members of industry, not just those who can't afford to do it on their own.

DR. GREENE: Jan?

DR. FRIEDMAN: I agree. I think that it needs to be stated very clearly. I don't think anyone is stupid enough to propose that this would be an activity that would exclude industry involvement, industry involvement and

planning in determining which studies need to go further, need to have a particular kind of additional assessment, we've got enough for this particular drug. Industry needs to be involved in all those decisions. They need to have the information so they can report it however they have to report it to FDA. They clearly have to be right at the heart of this activity. So, I don't think there's any question of diminishing their stewardship for the drug.

DR. GREENE: Let's move along here a little bit to the next question, which is what areas would need to be specifically addressed to ensure that useful information would come from such a centralized system. Sandra, as I read that question, I interpret that to mean specifically inclusion criteria for cases, exclusion criteria for cases, additional information that would need to be collected to address issues of confounding. Is that correct?

DR. KWEDER: No. Actually I think you've already touched on some of those areas. They're more general than that. It's probably not the sort of thing where one size fits all, but you've touched on some of them like protections for companies, protections for physicians who report, for patients. Many of them have already been raised. We're talking about sort of generic issues that perhaps even a workshop would need to begin to address. Another one that I might throw out is data ownership, data

control, that kind of thing.

DR. HOLMES: I could tell you from the AED pregnancy registry the system we've developed. We have a scientific advisory committee, that does not include anyone from industry, that's charged with deciding when something is ready to be released, being released in the form of an abstract at a meeting, a letter to the editor, a manuscript. This group sets the 95 percent confidence intervals that they want to see up front so that if you're going to say something is safe, you've met these criteria; if you're going to say it's significant, you've met these criteria. So, this would be the kind of thing a group would agree upon in a way that everyone would agree is free from bias but makes sense. Then from that, the information is released.

We have not released any information, so we don't have a track record in terms of what works best. Some people have argued that there should be a website where stuff is posted as soon as it's released. Some have argued that it should be letters to the editor. If you talk about manuscripts, you're adding several months at least to the interval between when it's developed. But that's what we came up with.

DR. GREENE: One question that I would like to ask is would there be anything attractive about a

centralized registry with respect to recruiting a comparison group or a control group or matched controls, people who are not exposed to your medication? Industry is clearly reticent to try to accumulate their own control or comparator groups. Would a centralized registry be attractive in that regard?

DR. ANDREWS: I think it's possible to generate some internal controls. As I mentioned yesterday, when we look across the registries, the different registries, that each use the same ascertainment method, the other registries can be the control group for a specific registry, and we are seeing very similar rates across registries. With the antiretroviral registry, we're able to use exposure in the second and third trimester as a comparison for first trimester exposure. So, I think there are creative ways that can be found.

I don't think there is any inherent reason that an industry sponsor study cannot collect a comparison group in a study that we conduct. I take the point that in terms of a adverse experience surveillance system, that type of system is not established to pursue a control group.

DR. GREENE: Let's see. Sandra, I think we've pretty well addressed that third bullet as well in our discussions so far.

So, if we can move on then to how can systems

and databases already in existence be better utilized in this effort, and what has been learned from existing methods? How can they be improved upon?

I think we've talked a bit about that as well in terms of what Lew has learned from the antiepileptic drugs database or the antiretroviral database, the Varivax database. I think we've learned a little there.

What further discussions are there on this point? Please.

DR. WEISS: We just finished a validation study looking at automated databases. It was very promising in that it is feasible and there are, for example, HMO databases and medical service databases that do have very good recordkeeping, pharmacy information, that you can use to start developing that.

The problem is that, one, a lot of these databases do not collect laboratory test results, and if we can encourage that information to become available in some way, that would facilitate this.

The other one is the collection of last menstrual period. In fact, the HMO we worked with has started that because of the results of the study so that they could look at this information.

And then the other one is that more databases do it so that we can combine them because no one by itself

is large enough and has enough pregnancies to do any one disease state in a reasonable amount of time.

So, those are the things that I hope we can find a way to encourage companies to do.

DR. GREENE: So, tell us a little more about the validation study that you did. Was this of an electronic database that was routinely used for medical care and you looked to see if the data was of research quality? Is that what you're talking about?

DR. WEISS: Yes, that's exactly what we did. We paired with an HMO and then we looked to see if we could identify things that would say a woman is pregnant early in her pregnancy and looked in the medical record to see was it complete, was it true, and then looked at people who had no indications of pregnancy to see were they really picking up all the pregnancies, and then looked backwards to people that had definite outcomes, live births, stillbirth, fetal loss, therapeutic abortion, see when we could have identified them very early looking backwards, trying to see how valid and reliable the data was. Like I said, it was very promising, but small numbers.

DR. GREENE: Any other comments on this issue? Please.

DR. CRAGAN: Sheila, did you have any information on patients moving in and out of the HMO

system? Particularly if we're looking at longer than just through the delivery process of following up children or identifying children with defects that you then look retrospectively. Do you have any information about how complete those records are over time as patient populations change?

DR. WEISS: That is a problem. Depending on the HMO, it obviously depends on kind of the rate of incoming and outgoing. We did find with pregnancies that there were markers with no outcomes and we did eliminate people who dis-enrolled, but we found that there are women who potentially have more than one insurance company, maybe through the husband and the wife, and so what you do is you do lose information not just because of switching but because they pick the other doctor through the other insurance to get their final care and you lose that.

DR. CRAGAN: Do you have any estimate of how large a part of the group you looked at that would be?

DR. WEISS: Call me afterwards. We'll look it up.

DR. GREENE: So, in terms of looking at automated databases, I guess that would begin to address number 3 here. In general, what other strategies might be helpful for collecting this information? Certainly there are other models in King County using pharmacy registration

databases that have been used successfully.

Other thoughts of other alternatives? Sandra, did you want to say something?

DR. KWEDER: It wasn't about this question. So, finish this.

DR. GREENE: Other thoughts? Allen?

DR. MITCHELL: Well, I mean, the bait was here. Other strategies, in parentheses, case-control, randomized controlled. I think that case-control designs and case-control surveillance are an incredibly useful resource and just ought to be in the mix.

DR. WIER: Mike, under the broader remit of other types of data as well, so far the discussion of pregnancy exposure registries has rightly focused on the detection of adverse fetal outcomes. But of course, yesterday we were reminded by the speakers of the broader remit here to better understand the risks, as well as the benefits, for drug use in pregnancy. But of course, we all recognize that cohort studies in pregnancy are rare or even unlikely for a variety of reasons.

So, while appreciating that an exposure registry is not even close to being any kind of an efficacy trial, I just have to wonder if the health care provider is contacted to ascertain the fetal outcome, what prevents us from asking about the therapeutic benefit? In other words,

if we take it that in many cases an exposure registry is going to be a course measure for detection of an adverse effect, is it untenable to make it a course measure of therapeutic benefit as well?

DR. GREENE: Jan?

DR. FRIEDMAN: To follow up on Pat's point, one of the issues that clinicians often face is which drug should this patient use for whatever it is she has to be treated for. She does need treatment. She has severe depression. She has seizures. She has a disease that requires treatment. Which drug among those that are available is the safest?

An alternate approach to looking at that is by selecting cohorts that have the disease. There are studies in the literature, most of which are just awful, of patients who have been identified with particular diseases and outcomes. There are groups there who could be studied. The AED registry may be an example of approaching this in a more effective fashion, but one could envision the same approach for people with various psychiatric diseases, various infectious diseases, various diseases, inflammatory diseases. I think that's another approach that we haven't really talked about. It provides a different kind of a study and often a lot of exposures to various members of a class of drugs.

DR. MITCHELL: I see that as a dramatic change in mission.

DR. FRIEDMAN: It's different.

DR. MITCHELL: Well, it's seductive as can be. I think that if you look at the quality of the data -- I mean, let's say we did that for Bendectin. What would we find compared to clinical trial data? I think that's the height of anecdotalism with an awful lot of terribly subjective endpoints, in fact, almost entirely subjective endpoints. It seemed to me that the charge of these two days was to look at risks, and the opposite of risk is safety, but efficacy was not in the picture. I don't know how the agency feels about it, but from a study design standpoint, I think it's a very dangerous step from one mission to another and one that I don't think can be accomplished.

DR. MONTELLA: Take that one one further, though. What if you looked not just at Bendectin, but what if you looked at Bendectin and chlorpromazine and metoclopramide?

DR. MITCHELL: Then do a clinical trial because my guess would be that the women who failed Bendectin would be put on chlorpromazine.

So, it's a complicated picture. I just think it's a very different mission.

DR. MONTELLA: And that's the real problem because the real problem is that the people who are writing the texts and talking to the patients and trying to answer physicians' questions about what they do are answering them in this way. They're selecting drugs in a class of indications and that's why Pat's question was so appealing to that group. So, it may be a worthwhile question to try and answer.

DR. GREENE: Patrick, I'm just concerned that you're not going to get data. You're going to get testimonials, and I'm not really sure that's going to be very helpful.

Sandra?

DR. KWEDER: Mike, you brought up yesterday -- and I think this speaks a little to what Patrick was getting at -- setting aside efficacy, looking at would it be reasonable to consider collecting information about maternal safety. I'm thinking you brought up yesterday the risk of hepatotoxicity, things where there are potentially objective measures of that, at least for hypothesis generation in the course of collecting information about fetal outcome. Would people be more comfortable with that?

DR. GREENE: Jim?

DR. LEMONS: Well, I agree with what Allen said. But it gets back to the primary intent of the

pregnancy labeling and the mind set. Is it a margin of risk or is it a margin of safety? I wouldn't, I guess, out of hand toss out the possibility that there could be some effective questioning regarding efficacy, but probably it will come down to more of a safety definition.

I know originally I was saying that the central registry or repository of information or surveillance system could distance industry from being the fox watching the henhouse, and I know that there is a lot of stewardship. I know this is a lot of perception and it may not be true. For me, I have the perception, so for me it's true. I think there is a perception of ownership that could lead to bias. It's I'm sure not true but it's there. Having some creative relationship, like Allen said and Jan said, I think the doors are wide open. I think the FDA could come out with some assurances that would involve and retain the proprietary stewardship of a particular company for a particular product and still come up with something very creative and positive.

But I think looking at this in a broad way and looking at the possibility of defining efficacy would be very attractive to corporate interests while you're also obtaining safety and risk data.

DR. MONTELLA: If you're doing a risk-benefit, you have assess benefit too.

DR. GREENE: Jim?

DR. MILLS: I think in terms of all of these issues, for maternal safety, the most obvious thing is you'd have to know a great deal of clinical information about the woman in order to interpret that so that you're making it a very complicated data gathering exercise.

For drug efficacy, likewise you need to know a lot about the clinical situation. You probably need laboratory data. Even assessing something like acne, you'd want to know what the acne was like before you started and what it was like when you got done with the treatment. In the best case, if you were trying to do, rather than drug versus no drug, a comparison among different drugs might be possible in an antiepileptic study, say. You'd still have to answer the big question why did the doctor start out with this drug as opposed to some other drug. Was it an equipoise situation in terms of the severity of the disease and just a random selection of drugs? So, for once I'll agree with Allen and say that I think it's a tough row to hoe.

(Laughter.)

DR. WIER: If we come back to the concept that in principle an early study like this is detecting signals, so you can turn this around to say I'm not trying to set the expectation for the benefit assessment any higher than

the expectation for the assessment of risk. You're looking for a signal. Even asking a simple question like did you find it necessary adjust the dose in pregnancy, I'm not saying that proves anything about efficacy. I'm saying it probes for questions that suggest further studies that could be warranted. It's a place to start.

It's just hard for me to imagine -- and I'm not in a position to do this, so understand I'm guessing here -- being in a situation where you're asking the care giver about the fetal outcome and that you just full stop at that point and not even ask what was your experience in terms of the therapeutic benefit of the drug. And did you find it necessary to adjust the dosage? Did you find it necessary to change therapies because it became ineffective in pregnancy? Things like this.

So, I hope the suggestion was taken in the right light to having really minimal expectations, not seeking proof in any way.

DR. ANDREWS: I think a couple of comments. I think there are many, many different models of industry and external collaboration, just many examples of that. One of the things that has been a very helpful model for us in the registries that we've conducted in house and now contracted out to PharmaResearch is to have the industry folks, as well as CDC, NIH, and others as an advisory committee to be