on people when you feel as if you have gone as far as you can go with that system to try to identify a problem.

DR. MITCHELL: The answer to the first question is how long should they go, and I don't mean this facetiously. A little longer is the answer. No matter where you are, there's going to be a voice that says let's go a little longer. So, I think your question cuts to the quick. You've got to set some criteria.

I would not suggest folding the tents on a registry at 100, and I hope no one interpreted these comments to suggest that.

I can't give an answer. So much depends on what your priors are, what the hypotheses are, what the outcomes of interest are. If someone is going into a pregnancy registry concerned about fetal varicella, that's a very specific outcome. If one is looking to assure the prescribing and public community about a drug's safety, however we want to avoid that word, then it's a very different message and a very different process. So, I'm being deliberately unresponsive because I don't know the answer.

DR. GREENE: But when you say how long you're going to go, you mean long in numbers or long temporally? Because obviously, that's going to depend upon the frequency of the exposure.

DR. MITCHELL: Right. One of the comments that I was going to make earlier was that in some of these scenarios we're painting ourselves a picture where we'll follow the drug until it's no longer used. At that point, the information becomes of historical interest but not of clinical interest. Drugs tend to have life cycles. Although as Karen points out, you get alpha methyl dopa that may arise from the grave, but by and large, that's what I think has to be put into the equation. If I were responsible for deciding about a registry where a drug at the outset of the registry was being used by 3 percent of women and now it was being used by virtually none and we're dealing with finite resources, I'd say, well, as a public health and clinical matter, I think we need to shift those resources into an up and coming drug.

DR. GREENE: Thank you.

The final speaker for the afternoon will be Dr. Rogers, who will talk about informed consent, please.

DR. ROGERS: Good afternoon. Is there anyone in the room who doesn't envy me being the last speaker talking about the Code of Federal Regulations?

(Laughter.)

DR. ROGERS: I've entitled this Individual Privacy and the Public Health. What is the good balance? I chose this title and posed the question about balance

specifically because I think the interaction between individual privacy rights and the public health needs to be carefully evaluated to strike that balance that best serves society while at the same time protecting the interests of the individual.

We've viewed the area of drug safety as a surveillance issue in this country as the public expects an alliance among prescribers, sponsors, and government officials to protect them from unsafe pharmaceuticals. But the definition of research in the Code of Federal Regulations would encompass the activities that are involved in our efforts to identify unsafe drugs, and this pushes the assessment in a totally different direction.

Today I will review the basis of the code and its provisions and explore the course of the deliberations of the advisory committee to the Antiretrovirals in Pregnancy Registry.

First of all, though, because HIV is my case study here, I'd like to make a few points about HIV.

HIV infection in women occurs predominantly in racial and ethnic minority populations who reside in urban areas in the rural south, who are not usually aware of their HIV status, who have many unmet socioeconomic needs, and are cared for in resource-poor, understaffed hospitals or public clinics. So, to place this discussion in

clinical context, I will eventually come to the very specific experiences of having served as government staff to the Antiretrovirals in Pregnancy Registry, or the APR, from 1993 through 1999.

Not only are these particular characteristics important, but the other thing that one has to note about this, choosing HIV infection in pregnant women as a case study, is that their pregnancy represents a situation in which the Public Health Service is actively encouraging and promoting drug exposure during pregnancy. So, the importance of obtaining safety information is really quite important.

The features of the APR were that it was initiated in 1989 to examine the effects of inadvertent exposure, and while it was originally intended to capture inadvertent exposures, the exposure status became intentional after the results of PACTG 076, which was the successful trial to interrupt perinatal HIV transmission, and finally to the latest PHS guidelines in which pregnant women are to be treated first for their own conditions.

It was modeled on the acyclovir registry that Dr. Andrews spoke about this morning. It was prospective in nature; that is, it collected both numerator and denominator data. The collection of the denominator data is the key component since it means the data were collected

on births to women who had not experienced a reportable adverse drug event.

In the registry, the staff interacted only with obstetrician reporters, and this design feature prevented the need or omitted the need for disclosure of identifying information as the child's care moved to the pediatrician.

No informed consent from women was obtained because there was no need for identifying information, and indeed no IRB review occurred. This was reviewed frequently by the advisory committee who continued to believe, up until relatively recently, that this was a surveillance activity which was conceived of as an extension of the spontaneous reporting system of the FDA.

The limitations of the APR. Interacting only with the obstetrician meant that we only received reports of structural defects that were apparent during the immediate postpartum care of the mother. It relied on voluntary reporting of very busy and stressed clinicians. And it could not be promoted by the sponsors, and consequently, very small numbers were enrolled.

At the same time, we had really compelling needs for data. The results of PACTG 076 and its implications for care required a balancing of information that clinicians would give to pregnant women when they were counseling them about making the decision to take

antiretroviral therapy. Our recent PHS guidelines for the treatment of pregnant women really encourage, and, in fact, we in the federal government have supported initiatives to promote the implementation of 076.

There also is the inadequacy of the safety data on fetal exposure to antiretroviral therapy during pregnancy, and we also have had recent scares. Some information a few years back emerged on very low birth weight infants who had been exposed in utero to antiretrovirals and then the mitochondrial disease that was reported by the French last year.

So, really where we find ourselves is we're looking at whether we're doing public health surveillance or whether we're doing research.

The counsel of the APR's advisory committee, prior to 1998 when it really became crystallized to the advisory committee, was that the APR activity constituted surveillance not research, and it was uniformly viewed by the committee that the APR was an extension of the spontaneous reporting system for adverse drug events.

The advisory committee strongly discouraged staff from accepting any patient names unless no other way to receive the report was apparent. This was consistent with sponsor practice around receiving other adverse drug event reports.

The feedback from clinicians was very important. Many staff members were interacting with reporting physicians in those understaffed hospital, inner city and rural clinic/hospital structures where the infrastructure was clearly inadequate, and the response back to the committee through staff people was that if there were a requirement for any other additional burden, other than providing the information, the information would not be forthcoming. They had difficulty in accessing charts. They had difficulty in making sure that patients were seen in a timely fashion, and they usually were quite understaffed.

This issue and these deliberations were revisited every time the APR advisory committee met.

But in the end the assessment came down to what kind of activity was the APR. In behalf of adverse drug reaction reporting, it did collect ADE data. It interacted with the clinician/prescriber as the spontaneous reporting system does, and it was fulfilling regulatory requirements in collecting information on adverse drug events.

What made it different from regular adverse drug event reporting, however, was that by including a denominator, it collected information on women who did not have adverse drug events but simply had exposure, and it provided regular summary reports to clinicians.

So, at this time, given that background and that context, of that case study and where we found ourselves, I'd like to now really bore you to death with the Code of Federal Regulations.

The definition of research. "Research means a systematic investigation, including research development, testing and evaluation, designed to develop or contribute to generalizable knowledge. Activities which meet this definition constitute research for the purposes of this policy, whether or not they are conducted or supported under a program which is considered research for other purposes."

This is extraordinarily broad, and this definition must be applied to all federally funded efforts.

Furthermore, if an institution is receiving federal funds for any research efforts and has a multiple project assurance, these regulations are uniformly applied to all of its research activity.

I'd like to just tell you what the basis of the code is. It is linked to the Nuremburg Code and to the Declaration of Helsinki. Both the Nuremburg Code and the Declaration of Helsinki are alike in their instance that subject autonomy be respected and in their elevation of concern for the rights of the individual above scientific and societal goals.

Specifically, principle 5 from Helsinki says that every biomedical research project involving human subjects should be preceded by careful assessment of the predictable risks in comparison with foreseeable benefits to the subject or others. Concern for the interest of the subject must always prevail over the interest of science and society.

Principle 6 says, the right of the research subject to safeguard his or her integrity must always be respected. Every precaution should be taken to respect the privacy of the subject and to minimize the impact of the study on the subject's physical and mental integrity and on the personality of the subject.

What you see is a very strong theme in the declarations that I've just pulled out, the principles I've just pulled out. That theme is that individual rights prevail over societal goals.

This is very different from regulations that come out of state law that really address communicable disease surveillance and investigations. They would emphasize society's benefits over individual rights in order to prevent transmission. In fact, to some extent in terms of adverse drug event reporting, we have expected that the information from individuals would be gathered to serve broader societal goals.

In the Code of Federal Regulations, there are categories of research. One is exempted research. In exempted research, what we have is, in order to qualify as exempted research, there is only involvement of human subjects in research that involves a collection or study of existing data, documents, records, pathologic specimens, or diagnostic specimens, if these sources are publicly available or if the information is recorded by the investigator in such a manner that subjects cannot be identified directly or through identifiers linked to the subjects.

This does not happen in any of the registries that we have because there are specific coded subject identifiers that -- with some effort in most situations, but there can be a link back to the subject from which the information is being collected. So, I don't think that in terms of any of the registry formats that we've discussed this morning and for the APR that it can be considered exempted research.

Another category of research is expedited research, and this category refers to research activities which involve no more than minimal risk and in which the only involvement of human subjects will be in one or more of the following categories. There are a number of them, but number 8 is relevant to our discussion. Number 8 says

the study of existing data, documents, records, pathologic specimens, or diagnostic specimens.

What is very important here is that the term "minimal risk" is suddenly in the mix, and let me tell you what the definition of minimal risk is in the code. That is those activities which an average person encounters during an average health care visit or in the course of average daily activities of life.

It is not a sliding scale so that you can say, oh, these are inner city women with HIV infection who live in communities where there is a great deal of violence and drive-by shootings, and therefore the risk that's allowed for these women is considerably more than the risk allowed for a housewife in Utah. That's not what minimal risk is. It is not a sliding scale. It is the average.

So, for it to be expedited research, it does have to meet that bar of minimal risk, and it does have to be preexisting information, information that's collected not specific for the purpose of the study but being evaluated like a secondary analysis.

Much of the registry activity could be conceived of as expedited research for many of the drugs that we've discussed today. However, it's very unlikely that any institutional review board would view our APR as expedited research because it's dealing with HIV infection

and HIV infection, because of the increased sensitivity around inadvertent disclosure, represents a special case.

I want to talk about the issue of informed consent and to tell you in the code what items have to be addressed in an informed consent and what items an institutional review board would be looking at in order to make sure that an informed consent is adequate.

These are the required elements. The purposes, the duration, and the procedures of the study have to be disclosed. Any foreseeable risks or discomforts, reasonably expected benefits to the subject or to others, the disclosure of any alternative procedures that would be available to the subject that he or she could access without being in the study, the confidentiality measures that the investigators have put into place to protect the subjects, compensation, if any, for injury that might occur as being part of the study, contact people for the study in case there are questions or concerns, and the fact that participation is voluntary.

The IRB may also require some additional elements. These would be risks to the fetus, circumstances under which participation may be terminated, additional cost to the subject that that subject would incur by participating in the study, the consequences of the decision to withdraw from the study, which should be none,

new findings that may emerge from the study would be provided to the subjects, and the approximate number of study subjects.

Therefore, we're looking at a rather large number of items that are either required or could possibly be added at the discretion of an institutional review board. The consent process, when it is informed, may be a prolonged process.

What we have for a registry like the APR -- and other registries may have the same concerns -- is the fact of the feedback we've gotten from the clinicians who are in the inner cities and in the rural clinics that are understaffed, that this additional process, superimposed on the consent that they are required to give by state law for HIV testing and for the regular care, the issues that are involved in the regular care of pregnant women -- superimposed on that and in addition to that, many of the clinicians also do get involved in some of the perinatal transmission trials, that this is such an additional burden, that reporting wouldn't happen.

In that instance and because of that consideration, one of the things that can be done is a request for a waiver of informed consent. This is allowed under Code of Federal Regulations, 46.116(d). These particular requirements have to be met. The research can

be no more than minimal risk, which I defined before. The waiver will not adversely affect the rights and welfare of subjects. The research could not be practically carried out without the waiver, and whenever appropriate, the subjects will be provided with additional pertinent information after participation.

So, given all of this information that I've shared with you, the advisory committee to the APR, seeing that there was a growing focus on institutional review of projects, the fact that this project fell under the Code of Federal Regulations definition of research, and the involvement of federal officials on the advisory committee, the advisory committee in 1998 recommended that the registry protocol be submitted for IRB review.

We also recommended that all data be collected anonymously and coded, that the reporting forms be revised because of the way that they had collected information, and we recommended that they seek a waiver of informed consent.

Seeking a waiver of informed consent really depends on the study design, which of course follows the study question. For the APR, who is simply looking at structural defects with the potential for detection only during the perinatal period, the waiver seems to be an appropriate mechanism.

Finally, the last slide. The experience of the

APR I wanted to share with you in their efforts to seek this IRB review. They've approached several major universities, all of whom refused, citing that they had their own institutional overload with their own protocols, and they questioned their authority and their jurisdiction to be doing a review for a registry supported by sponsors.

Private IRBs -- and there are a few across the country -- required an unreasonable fee to review.

I had an off-the-record discussion with OPRR about exploring whether the APR could establish an IRB of their own. What we were trying to see was if OPRR would issue a single project assurance and allow them to establish their own IRB that would review. OPRR said that because there was no federal funding involved, they really had no jurisdiction to do that, and besides, they were very busy too.

So, finally, what the APR is doing is the second option up here. They're collecting that unreasonable fee from all of the cooperating sponsors and moving forward.

I think in summary I wanted to make five points, and I'll make them quickly.

Efforts that collect denominator or exposure information essentially move outside the standard and traditional adverse drug event reporting. I think that's a

very clear conclusion to make.

The second point is that to maintain public trust and confidence, information on women and pregnancy outcomes must be carefully protected.

The third point is that this protection is best ensured by external and objective review of procedures that are in place.

The fourth one is using the Code of Federal Regulations and the IRB structure that's in place seems to be the best vehicle for accomplishing the protection. It is established, accepted, and known.

And five, requesting the waiver of informed consent is an option. It is very study-specific and really requires a compelling justification to occur.

Thank you.

(Applause.)

DR. GREENE: Thank you.

This presentation is open for discussion or questions, please.

I have one question with respect to guaranteeing the confidentiality of data. It seems as though as time goes on, we realize that less and less is really confidential and really protected. The specific example I guess that I would cite is one recent experience of Dr. Sharin Gabriel in Minnesota. She collected data

which suggested very strongly that there was not, in fact, a relationship between silicone breast implants and rheumatologic disorders. In the course of the lawsuit that the plaintiffs brought against the companies, her data which suggested there was no relationship was subpoenaed. She found herself in a position of either refusing to comply with the subpoena and possibly facing criminal pains or trying to fight the subpoena for which she had no money or agreeing to hand over the data and violating the pledge that she had made of confidentiality to her subjects or abandoning her research and agreeing never to publish the data. It was a conundrum that she faced and she elected just to agree to never publish the data and to basically bury the results.

What reassurances are there that should there be determined and clever attorneys, that this data will remain confidential?

DR. ROGERS: And you want me to answer that. They subpoenaed names?

DR. GREENE: They subpoenaed her entire database.

DR. ROGERS: I think one critical piece there that seems to be missing for me is, did she put specific identifying information in her database or did she keep that separate? I think IRBs are very careful to have

separate records for clinical shadow records, and there should only be a subject IDs in a database. I think one should be making a distinction in practice and one could make a distinction legally in what one surrenders.

DR. GREENE: Well, I think most researchers will tell you that if you're collecting enough demographic information about patients, you only need a half a dozen fields that are sufficiently unique that you can pretty figure out who the individuals are whether they're specifically identified or not.

DR. ROGERS: Again, if I were in that position and I were concerned, I would have not only my identifying codes locked over here, but I also would have two subset databases that I could merge on an ID, one with those identifying information -- I mean, there are levels of individual protection I think that one could undertake to prevent one's self from being in that situation.

It's wonderful to do that on Monday morning, but I think if we could all learn a lesson from the terribly unfortunate experience that she's had, it would be to put those kinds of layers of personal and subject protections in order to do that, to be able to give that kind of guarantee of confidentiality.

DR. GREENE: Allen.

DR. MITCHELL: I'm not sure that I agree that

the layers -- they offer some protection, but there's no reason the attorneys can't go after every aspect of it.

I would offer two responses to that situation, Mike. First of all, I gather she was not part of an institution. But we've had that situation where we've had data subpoenaed and we fought the subpoena. I think it's very common for academics to roll over when they receive a subpoena. Whether she did or not, I would urge people who are confronted with subpoenas not to roll over and to seek institutional support.

The other is a federal certificate of confidentiality, which seems to me very relevant. It's something we've gotten in our studies where we have sensitive information. CDC has done that as well in its study and it provides substantial protection.

DR. ROGERS: Well, actually I'd have to correct that.

DR. MITCHELL: Am I wrong?

DR. ROGERS: We all think it does. It has never been tested.

DR. MITCHELL: I'm sorry. Yes, I'll qualify that.

DR. ROGERS: It makes us sleep easier.

DR. MITCHELL: But at least conceptually it offers a layer of protection that would at least make some

attorneys think twice about going after the data and does put the federal government on the line. I think that some courts might view that as a higher authority than simply what we would consider a contract between us and the patient, which we would consider inviolate and a higher authority than any subpoena, but the courts may not agree.

DR. ROGERS: Right. I think too the institution would have to have some relationship with the federal government in order to obtain one for data.

DR. MITCHELL: No.

DR. ROGERS: Well, in our experience it has been study-specific.

DR. MITCHELL: Yes. Oh, it's study-specific, for sure. But it only requires a demonstration that there's some sensitivity to these data.

DR. ROGERS: And federal funds not involved?

DR. MITCHELL: That's correct. I'd have to look but I think that's correct. I'm not sure, Audrey.

DR. ROGERS: I'm not sure either.

DR. GREENE: Yes. In this particular case, she was part of an institution. She went to the institution and they said we don't have the money to fight this. It could be many hundreds of thousands of dollars and there's no guarantee of success.

DR. MITCHELL: That's why they get overhead

rates.

(Laughter.)

DR. GREENE: Dr. Kweder, you had a question, comment?

DR. KWEDER: Yes. Audrey has made the comment that when you begin to collect denominator data, you move quickly out of the realm of traditional post-marketing surveillance. I think we have to think carefully about making that sort of a general statement. I think in many respects the kinds of registries we're talking about really are hybrids.

One reason to think carefully about that is that historically we have considered data that comes to us from standard post-marketing surveillance, protected information, and where courts have sought to seek identifying information about those individual cases, the FDA has been very rigorous in defending and protecting that information so that the courts couldn't take on and use or lawyers couldn't take on and use that information in malpractice cases or in other types of injury cases.

When MedWatch was developed, one of the things that FDA did to try and encourage more reporting was develop a regulation that specifically extended the same kinds of protections to cases that we received from the industry. That was a very important step because

previously those protections only covered practitioners who reported to the agency directly, but we developed a regulation to extend that. And it is something that we may need to think about how that applies to registries as well.

DR. ROGERS: Yes. The distinction I was making was not the classic case report. I think with the Office for Protection from Research Risks moving from the Office of the Director of NIH to Under Secretary level in the Department of Health and Human Services, that the FDA and the CDC, as well as NIH -- all of the activities will be more closely scrutinized. I think it will serve us all well to understand what their definition of research is.

DR. ANDREWS: I'd like to make a comment basically echoing Dr. Kweder's comment that it may not be crystal clear what falls under the definition of research versus surveillance. One could certainly make a case that certain types of registries more appropriately fall under a definition of broad public health surveillance and a number of organizations, including ISPE and PhRMA have suggested to HHS in response to their regulations on data privacy that these kinds of surveillance programs be considered under the surveillance definition for purposes of being able to collect data without these potential barriers.

But I think it's an open question and there's really no clear answer. Part of the reason there's no

clear answer is the point that you illustrated well, Audrey, and that is, IRBs have not yet developed a mechanism for evaluating privacy risks uniformly across the country.

I think that it would be very useful for additional training to be available to IRBs so that when they're looking at studies where the primary risk to patients is a breach of confidentiality, that the use some standard and consistent measures, which just aren't there now. Researchers should never be in a position of shopping for the appropriate IRB to review a study.

DR. ROGERS: I would strongly encourage the committee, as it deliberates, to consider interacting with an organization called Public Responsibility in Medicine and Research, which is the professional educational organization for IRB members. We took on an aggressive educational campaign around adolescent participation in research, which if you think you're in trouble, you might try that. It's worth the investment in trying to educate them through that organization.

DR. GREENE: Yes, please.

DR. SHARRAR: I'd just like to make one additional comment. Part of the problem is that when you're dealing with HIV infection, you're dealing with a disease that has all other sorts of confidentiality

ramifications.

DR. ROGERS: Absolutely.

DR. SHARRAR: This is not a normal disease process nor a normal registry.

DR. ROGERS: Absolutely. I'm glad you emphasized that. I tried to make that point.

DR. GREENE: Other questions? Dr. Kweder?

DR. KWEDER: I actually thought that maybe Lew Holmes could comment on his experience using informed consent as part of your study or registry and sort of the pros and cons of that.

DR. HOLMES: You mean in terms of the institution's ability to understand what we're doing or the problems with the women themselves?

DR. KWEDER: Both.

DR. HOLMES: I bring up the institutional issue because I work at a big university hospital. When we said we were going to set up this pregnancy registry, they were not immediately accepting of why this made any sense as an activity to do at the hospital. One of the problems is IRBs contain an incredible spectrum of people who do different kinds of work, and I think just by chance, we might have gotten somebody else who had no trouble with it, but IRBs are made up of an interesting spectrum.

We're at a time when our IRB process -- and I

suspect everybody else at universities would echo this -- are very slow and lumbering because of the hot button issues of confidentiality. If you ever take a blood sample, heaven help you, because the DNA issues slow your process down to a snail's pace. The fact that your approval for last year ran out six months ago is your problem, not theirs.

Coming to the women themselves, the IRB has standard paragraphs that they insist are present in consent forms. When you look at a registry that doesn't have a lot of the components that would require those paragraphs -- like for example, if you're injured in the process of participating in the study, we will pay for your care -- well, that kind of thing makes the form longer, and the longer the form, the more it puts off the woman who is reading it, even though the content might not be worrisome. So, it has not been an easy step.

We have not found very many women actually read the thing and close the door and say, forget it, I'm not going to do this. But there is a small group, probably less than 1 percent, who when they see the consent form, that's it. So, it's not a trivial issue.

I think Don has talked about biomarkers, as should be discussed, because I think this whole work has got to go in the direction of biomarkers. Clearly, there

are going to be DNA-based markers that will pick out the high risk and low risk people. That's clearly where we're going, but that is the same path that the public is scared about and the IRBs are scared about.

So, it's complicated now. I think it's just going to get more complicated.

DR. GREENE: Any other comments?

(No response.)

DR. GREENE: Well, a few announcements before we finish up.

DR. TITUS: I just want to address a couple of things. Tomorrow's meeting starts an hour earlier, so please be here at 8 o'clock.

Regarding dinner tonight, most of you are going to dinner. We have a van arranged to take you there. It can only hold about half of you at one time. The first van is going to try to leave at 6:30, and the second van will leave 15 minutes later. But you all can't be in that second van. So, somebody has to come down and mill around and socialize. So, I would encourage you all to come down at 6:30. You're really welcome to dress casually. There's no reason for you to go dressed up. You can be normal. You can dress down.

See you tomorrow morning.

DR. GREENE: Thank you, everyone.

(Whereupon, at 4:48 p.m., the subcommittee was recessed, to reconvene at 8:00 a.m., Wednesday, March 29, 2000.)

- B -

- C -

- D -

- E -

- F -

- G -

- H -

- I -

- N -

- O -

- P -

- S -

- T -

- U -