42nd MEETING

NATIONAL BIOETHICS ADVISORY COMMISSION

Hyatt Regency Bethesda
One Bethesda Metro Center
Wisconsin Ave. at Old Georgetown Rd.
Bethesda, Maryland

Volume II

July 11, 2000

Eberlin Reporting Service
14208 Piccadilly Road
Silver Spring, Maryland 20906
(301) 460-8369

I N D E X

I N D E X (Continued)

P R O C E E D I N G S

ETHICAL AND POLICY ISSUES IN THE OVERSIGHT OF HUMAN SUBJECTS RESEARCH

PANEL IV: IDENTIFICATION AND ASSESSMENT RISK AND BENEFIT

DR. SHAPIRO: Marjorie?

DR. SPEERS: We would like to begin with our fourth panel under the topic of our oversight project. This panel is addressing issues related to the identification and assessment of risk and benefit in research.

Dr. Ernest Prentice will be presenting his paper that we have commissioned from him, which is entitled "Institutional Review Board Assessment of Risks and Benefits Associated with Research."

Just to remind you that we had originally commissioned two papers. One paper was to deal with philosophical issues. The other paper was to deal with practical issues. Dr. Prentice is going to be presenting from a practical perspective, from that of an IRB chair or co-chair in his case but with many years of experience of looking at how IRBs examine risk and benefit and the risk/benefit ratio.

Thank you.

ERNEST D. PRENTICE, Ph.D.,

ASSOCIATE DEAN FOR RESEARCH,

CO-CHAIR, IRB OFFICE OF REGULATORY AFFAIRS, UNIVERSITY OF NEBRASKA MEDICAL CENTER

DR. PRENTICE: Well, good morning, Mr. Chairman, commissioners, IRB colleagues and public representatives. If I may, I would like to address the commission from up close to the screen.

DR. SHAPIRO: By all means, whatever is most convenient for you.

(Slide.)

DR. PRENTICE: As you know, the title of this paper is "IRB Assessment of Risk and Benefits Associated with Research," and I would like to thank the commission for the privilege of writing this paper.

I would also like to acknowledge my colleague, Dr. Bruce, Gordon, who is co-chair of the IRB, who assisted me with this authorship.

(Slide.)

I believe that this is the IRB's cardinal charge: To determine that the risks to subjects are minimized and are reasonable in relationship to anticipated benefits.

(Slide.)

And to accomplish this charge we need to ask the question how should an IRB assess the risks and benefits associated with research.

(Slide.)

There are seven basic tasks that an IRB should perform.

First, to identify the risks, quantify the risks, classify the research utilizing this risk threshold called minimal risk, ensure that risks are minimized, identify the benefits, perform a risk benefit analysis and perform ongoing assessment after the research is approved. So I am going to be talking very briefly about each of these and they are reflected in the paper.

(Slide.)

First, identification and assessment of research risks. That is -- look at that.

(Slide.)

What is the definition of risk in a research context? In order to address this issue we need to go back to a medical malpractice case, Canterbury versus Spence, that established the reasonable person standard. So a material risk is one that a reasonable person, in what the physician knows or should know to be in the patient's position, would likely consider to be important in deciding do I want to participate in this research or not or rather in the therapy or not.

(Slide.)

Now the National Commission, of course, reviewed this particular case and they felt that the

reasonable person standard was not sufficient for research participation so they established what is called a reasonable volunteer standard, i.e. the research subject being, in essence, a volunteer who may want to know a lot more about the risks associated with research than they would if they were simply trying to decide whether or not to participate in a therapeutic intervention that is considered standard.

(Slide.)

So if we take the reasonable volunteer standard and we incorporate that into the definition of risk, we come up with something like this. A risk is a potential harm, discomfort or inconvenience that a reasonable volunteer, in what the investigator knows or should know to be the subject's position, would likely consider significant.

So we recommend on our IRB that we utilize a reasonable volunteer standard even though this is not reflected as such in the federal regulations.

(Slide.)

We believe that IRB members, and certainly investigators, should identify and assess the importance of research risks from both a scientific perspective, and by placing themselves, insofar as possible, in the average subject's position and this

is not always easy. So you need to take a look at the protocol, look at the eligibility criteria and try to place yourself in the position of a subject in that protocol.

For example, let's say an investigator is doing a cardiac risk study and they are looking for volunteers that may have a certain profile that would lead them to be susceptible to coronary events. Well, this might be an example of one such couple.

(Slide.)

I like to show this slide. It is kind of humorous but the fact of the matter is that, while we may not agree with this kind of lifestyle, it may not reflect our own lifestyle, the fact of the matter is that the investigator and the IRB members should look at the lifestyle of the perspective subjects and review risks from their perspective. In this case probably even getting up and moving may be risky.

(Slide.)

Now there are five general categories of risk. The physical, the psychological, the social, the economic and the legal. Physical risks are usually easier to identify. I am not going to address those. Psychological risks are often more nebulous.

And let me just give you one example. In many clinical protocols, there are quality of life surveys attached to the clinical protocol. These quality of life surveys contain invasive, sensitive questions about lifestyle, the effect of the therapy on lifestyle and family dynamics. In many cases, there are risks associated with such surveys but they are not adequately addressed by the investigator and often they are overlooked by the IRB.

We heard yesterday about social risks, such as stigmatization associated with a community based research. There are economic risks and there are even legal risks that are addressed in the paper.

(Slide.)

Now this is what I refer to as a research risk umbrella and here again we see the five categories of risk and under this umbrella we also have inconvenience and discomfort. Sometimes we tend to ignore the fact that research projects may inconvenience subjects. They may have discomfort, but these inconveniences or discomforts do not rise to the level of a harm, and it is easy to overlook such.

For example, let's say a protocol involves asking a research subject to undergo an MRI. Well, anybody who has been in an MRI tube knows that you

are in this little tube and you have got to lie down and you have got to be very still and you hear this knocking noise, and certainly it is inconvenient, it is uncomfortable, and in some cases, if you are claustrophobic, it is going to rise to a level of harm.

So we need to be careful that we do not overlook this aspect of the research risk umbrella.

PROFESSOR CAPRON: Dr. Prentice?

DR. PRENTICE: Yes. Just to clarify, those three levels apply across the five types, is that what you are saying?

DR. PRENTICE: More or less but probably more in the physical category than in some of the other categories. For example --

PROFESSOR CAPRON: This is an interaction. This is a matrix.

DR. PRENTICE: Yes.

PROFESSOR CAPRON: Now IRBs often encounter difficulty in trying to distinguish risks when research is combined with performed concomitantly with therapy.

(Slide.)

So the question arises, when research is combined with standard therapy, the subject would receive, regardless of participation in the study, what risks should be considered by the IRB, what

risks should be disclosed to the perspective subjects?

(Slide.)

Well, we know that the risk of standard therapy the patient would undergo independent, and I stress independent, of their participation in the research usually, not always but usually need not be considered by the IRB.

(Slide.)

For example, let's take a study where an investigator wants to perform hemodynamic measurements during standard open heart surgery. Well, in this particular case, usually only the risks of the measurements are germane to the IRB's review, not the risks of the open heart surgery.

(Slide.)

Let's take another example. A PET scan is administered to schizophrenic patients and they are already taking an FDA approved drug in order to assess the drug's effect on brain metabolism. So the research is the PET scan. The patients are already taking the drug so only the risks of the PET scan need to be considered by the IRB, not the risks of the drug.

(Slide.)

However, if we change the scenario around a little bit, and we say schizophrenic patients will

be given an FDA approved drug, they are not taking it yet but they are going to be given an FDA approved drug, even though the focus of the research is not the efficacy of the drug, our IRB would contend that you would include the drug in the risk/benefit analysis. But again that is not always clear, is it?

(Slide.)

Now after the risks are identified, we believe it is necessary to undergo risk quantification looking at the probability of occurrence, the magnitude of severity and the reversibility of any given harm, and quantify that if that is possible. That is not always possible but where it is possible it should be done.

We ask our investigators to provide us with data to that effect so that we can more fully evaluate the risks. Of course, some risks are simply unknown. They are unexpected.

(Slide.)

This is a humorous slide. He choked on a placebo. But it has a serious note and the serious note is this: The fact of the matter is that, in research we do not always know what the risks will be, and we need to advise prospective subjects of that fact.

(Slide.)

Now this is a very important part of the assessment of risk -- classifying research according to the minimal risk standard.

(Slide.)

The way in which an IRB interprets and applies the minimal risk standard, which is a threshold level of risk, is a major determinate in establishing necessary protection for human subjects. Under current regulations it is used to establish whether or not a research protocol can be reviewed by the expedited review method, whether or not informed consent can be waived, whether or not additional protections are necessary for vulnerable populations such as children. So it is a very, very important consideration.

(Slide.)

Now this is the definition of minimal risk in the current regulations. Minimal risk means that the probability and magnitude of harm, or discomfort anticipated in the research, are not greater than those ordinarily encountered in daily life or during the performance of routine physical and psychological examinations or tests.

Now what does daily life mean? Is it the daily life of a healthy person? Is it the daily life of a fireman or a policeman? Is it the daily life of somebody who lives in New York or somebody

who lives in rural Iowa? What are the risks of daily life? It is not easy to identify.

(Slide.)

In the preamble to the regulations, the framers of the regulations considered whether or not to tie minimal risk to the daily life of a healthy person, and they chose instead to reword the final regulations to reflect the intention that the risks of harm encountered in daily life means those risks encountered in the daily lives of the subjects of the research. That is a very, very important distinction.

(Slide.)

However, OPRR's current interpretation of the definition of minimal risk does not consider a relative standard. Rather OPRR has adopted an absolute standard which makes a big difference. So if we utilize the absolute standard and kind of qualify what minimal risk means in that context, it means that the harm or discomfort anticipated in the research are not greater in and of themselves than those ordinarily encountered in the daily life of normal healthy subjects. Normal healthy subjects or during the performance of normal routine tests that normal healthy subjects might undergo.

(Slide.)

So, for example, a normal healthy

individual obviously would never have a bone marrow biopsy. That clearly would be a greater than minimal risk procedure. However, utilizing a relative standard, a patient that has leukemia that undergoes multiple bone marrow biopsies, one additional bone marrow biopsy for nontherapeutic reasons might be considered to be minimal risk under a relative standard so it makes a big difference how you interpret minimal risk in terms of protecting human subjects.

(Slide.)

The next category is minimization of risk.

(Slide.)

The federal regulations require that risk to subjects be minimized utilizing procedures which are consistent with sound research design. I am not going to get into this now, but sometimes, in some cases, you have got a lot of conflict between the attempt by the IRB to minimize risk and sound research design. What comes to mind immediately is placebo controlled clinical trials. You are not minimizing the risk utilizing a placebo control in many circumstances but it may be the best scientific design so this is a problem that IRBs face.

(Slide.)

So how do we minimize risk? Well, there are a whole lot of things we can do. Certainly the

study personnel have got to be qualified. We need to have additional protections for any populations that are vulnerable. We need to substitute procedures, whenever possible, that have less risk or are going to be performed as part of the patient's routine care. We need to ensure that subjects are appropriately monitored, and that adverse events are promptly reported to the IRB and the sponsor.

We certainly heard a lot about that relative to the gene therapy problems lately. Subject withdrawal criteria are appropriate and the timely treatment plan is in place. I would contend that the IRB must ensure that all of these factors are considered during their review.

(Slide.)

Identification and assessment of benefits associated with research. What is the definition of benefit in a research context? Well, definition of benefit means that it is a valued or desirable outcome resulting from the research, a direct result from the research. And there are two types of benefits, direct benefit to the subject, and benefit to society. Certainly in all research there must be benefit to society because after all, the definition of research is activities designed to increase generalizable knowledge. But there is not always

direct benefit to the subject in research.

(Slide.)

Now after the benefits are identified, and they are maximized to the greatest extent possible through appropriate protocol design, the IRB engages in what is referred to as a risk/benefit analysis.

(Slide.)

Federal regulations require that risks to subjects be reasonable, reasonable, in relation to anticipated benefits, if any, and the importance of the knowledge that may reasonably be expected to result. These are interesting words, reasonable and reasonably.

(Slide.)

Now you might ask, well, how does an IRB perform a risk/benefit assessment. Well, it would be nice if we had a computer program, we could plug in some numbers on the risk side, some numbers on the benefit side and say, okay, it is -- we can justify the research. That is not the case and it is never going to be the case.

(Slide.)

It is much like the every day decisions that you and I make. We go down to the local greasy spoon for lunch, we take a look at the menu, we say, "Okay, what am I going to have for lunch today? Am I going to have the tuna salad?" The risk of the

tuna salad made with water packed albacore tuna and no mayo is that it tastes horrible.

(Laughter.)

Benefits: It is healthy. "Or do I have the cheeseburger and increase my risk for cardiovascular disease." That is the risk. The benefit is most people like cheeseburgers. I guess fortunately for McDonald's, Burger King, Pizza Hut and America's cardiologists most Americans make the wrong decision most of the time but we hope that IRBs try to make the right decision most of the time. So it is a judgment call.

(Slide.)

But not all risk/benefit analyses are easy. Some are very complex.

(Slide.)

For example, the Utah artificial heart experiment, December 1st, 1982.

(Slide.)

This is William Devries performing the first implantation of an artificial heart in Dr. Barney Clark, a 72 year old dentist suffering from cardiac myopathy. He had a cardiac output of about one liter. He was dying. There were no alternatives. There were no human hearts available so they implanted this artificial heart. He lived for 112 days tethered to a life support. Then he

died of multiple organ failure.

(Slide.)

And ethicists immediately began debating whether or not the risk/benefit relationship of this research was appropriate and we do not have time to go into all of these issues. I would just simply draw your attention to this one. Was the risk/benefit relationship acceptable from the individual as well as societal perspectives?

The societal perspectives become a very important consideration, much more so now than back in the early '80s because of such clinical procedures as xenotransplantation.

(Slide.)

Now we need to remember in clinical research, there are not guaranteed benefits. It would be nice if there were guaranteed benefits, but there simply are not.

(Slide.)

This is a slide showing Louis Washkansky who received the first human to human heart transplant December 15th, 1967. He lived for 17 days.

(Slide.)

Now if we had stopped heart transplants in the 1960s when the results were dismal, we would not have been able to give over 2,300 people last year,

a new heart and a new lease on life. So I think that IRBs must remember that.

(Slide.)

Then, of course, IRBs have to perform an ongoing assessment of research after the research has begun. That is called monitoring and continuing review. So you have got to ensure that the risk/benefit relationship of the research continues to be justified.

(Slide.)

And, of course, we know that IRBs have been criticized by federal regulators for not performing substantive and meaningful continuing review. That is a major problem for IRBs.

(Slide.)

I have some recommendations very briefly. They are in the report. I am just going to go through these very, very quickly. IRBs need to perform a thorough evaluation of research risks and they need to also consider risks that do not rise to the level of harm, and they need to ask the investigator the right questions, and use the investigator to provide the necessary information that they need to evaluate the protocol.

(Slide.)

We need more guidance concerning how we mesh consideration of risk related to therapy versus

research. That is not clear. That is probably why we have 20 page consent documents these days.

(Slide.)

Investigators should be required to quantify the risks. It is not a requirement right now. I do not know how many IRBs actually ask their investigators to quantify risks, but without quantification, if possible, you have no handle on the significance of the risk from either the IRB's perspective or subject's perspective.

(Slide.)

It seems to us that a relative standard of minimal risk is appropriate for research involving competent adults. Whereas an absolute standard with some limited relatively may be more appropriate for vulnerable subjects, such as children in research.

(Slide.)

And we believe that a mechanism should exist for IRBs to share with other reviewing IRBs significant findings which negatively impact the risk/benefit relationship of the research. We have taken it upon ourselves, when we have encountered a protocol that is a multicenter protocol that contains a number of significant ethical or regulatory problems, to contact other IRBs about our concerns.

(Slide.)

We think that there should be more DSMBs. They ought to be mandated. I do not know who is going to pay for them. I do not know where we are going to find qualified people to serve on them but IRBs need help. You cannot expect IRBs to act as DSMBs. We are not qualified.

(Slide.)

And, finally, the protection of human subjects is clearly an absolute obligation and it is an obligation borne by the investigator first, the institution, the IRB, and the sponsor with enforcement by FDA and OHRP.

(Slide.)

I think it is clear we can and should do better. Thank you for inviting me and I will return to the podium.

DR. SHAPIRO: Well, thank you very much.

I think we can turn -- whoever is in charge of the lights, we can turn them up. Maybe no one is in charge of the lights.

Marjorie, do you want to say anything before we go to questions from commissioners?

DR. SPEERS: No.

DISCUSSION WITH COMMISSIONERS

DR. SHAPIRO: Okay. Let's now go to questions and our comments from commissioners. Alex, and then Larry.

PROFESSOR CAPRON: A question of clarification, Dr. Prentice. You made the very important point, at the end as part of your recommendations, that the IRB should contact other IRBs with information. Have you run into problems with assertions of the proprietary nature of the results of research, including the risks or harms,or discomforts that turn up?

DR. PRENTICE: No, we have not. As you know, the regulations allow IRBs to seek consultation. That consultation can come from anywhere, including other IRBs. So we have not had a problem in contacting other IRBs and sharing some of our concerns and asking them to provide us with their considerations relative to the review of a protocol.

It does not mean that they are going to change their minds. As a matter of fact, the last time that we had this problem, we had a multicenter protocol that was already up and running at five children's hospitals. We felt it was an inappropriate protocol. We chose not to approve the scientific design. We wanted to alter the scientific design. I was quite surprised that the lead center agreed to allow the scientific design to be altered at our site. We felt that this was an appropriate thing to do.

PROFESSOR CAPRON: Are you referring then in that recommendation number 5 only to prospective issues? I had taken you to be also referring to things which occur during the course of research, where adverse events or the failure of an intervention to achieve the results that were predicted on the benefit side, would be information that you would share with other IRBs. Do I understand that as part of your recommendation?

DR. PRENTICE: I would say it is more applied to prospective research. I would think that the sponsor, whether that be a pharmaceutical company or NIH, would be -- or a co-op group, would be in a much better position to discuss those kinds of issues and share those kinds of findings with IRBs as part of the ongoing review of research. So I am really referring to the -- at the initial stages of IRB review, where an IRB is struggling to decide is this research something that should be approved.

DR. SHAPIRO: Thank you.

Larry?

DR. MIIKE: I have got a couple of questions. One is on the exempted research and the other one is about a consent process.

I assume that in your institution, your IRB is not the one that decides what is exempt or not,

and somebody else -- some administrator does that. My question is twofold on that. One is that, would you think it would be better decided by the IRB and, number two, is there a common misunderstanding about what is exempt or not from the experience from your side?

My informed consent question is triggered by your statement about a complicated issue requiring a 20 page informed consent document. We have heard from others that some people use sort of a little questionnaire to see whether prospective subjects really understand that they are getting into and whether that might be a useful mechanism in some circumstances.

DR. PRENTICE: All right. Let me address the first question. I do not think that the IRB itself should determine whether or not a research protocol is exempt. I think that competent IRB staff are perfectly capable of performing that particular function.

And, yes, there is a misconception as to what is exempt. Clearly when I have been on site visits and reviewed files of exempt protocols, they have not been exempt.

The exempt categories are problematic in some cases. Let me give you an example. Survey research, no matter how sensitive the survey is, if

there are no subject identifiers, it is exempt. Now I would contend that a sensitive survey involving sexual abuse, alcohol, drug abuse, spousal abuse, et cetera, even without identifiers, contains a significant psychological risk from the first moment that the subject opens up the questionnaire booklet and encounters that first question but, that is exempt. And technically there is no requirement for informed consent.

Our IRB would never exempt such a protocol. As a matter of fact, it goes to the full IRB, requires full informed consent but perhaps not a signed consent form for confidentiality measures.

So I think that the exempt categories need to be looked at again.

As far as your second question on concern relative to informed consent, we have over 1,000 research protocols and we are small compared to Minnesota or UCLA. It is not practical to administer a written examination to subjects but you do need to assess comprehension. We ask our investigators to specify in their application how they will assess comprehension.

We have only had two that have used a written examination. Most of our investigators question the prospective subjects with regard to their understanding, or they ask the subject to

reiterate in their own words their understanding of the research, and that is documented in the record. That is what we expect our investigators to do.

DR. SHAPIRO: Thank you.

Diane?

DR. SCOTT-JONES: I have a couple of questions about research with children. In your recommendations you recommend an absolute standard for risks in research with children and I agree that is very important. You also point out to us around page 9 of your paper that there is a lot of ambiguity and conflicting messages in the guidelines for research with children, and I would like you to say a little bit more about that and say what standard you think is applied usually in the review of research with children. Is it the absolute or the relative one?

And then my second question is whether you have given any thought on research with adolescents as distinct from younger children. Near the end of adolescence, the individual becomes able to consent for himself or herself. So have you thought how we might handle research with adolescents differently from research with children?

DR. PRENTICE: Let me begin with the first part of your question.

As you know, the regulations provide

additional protections for children as part of subpart D and there are four categories of research in subpart D. There is 404, 405, 406 and 407.

404 is research not involving more than minimal risk, and it is real easy to satisfy the requirements if the research involves no more than minimal risk assuming that you are correctly interpreting and applying that standard.

The 405 category requires direct benefit to the individual subjects. So you can have greater than minimal risk but direct benefit to individual subjects and the requirements are also easy to satisfy.

It is when you have more than minimal risk, no direct benefit to the child, that is 406. And then you have four requirements that must be met. And the first requirement, which is related to minimal risk, is there cannot be more than a minor increase over minimal risk. What is -- first of all, what is minimal risk? What is a minor increase over minimal risk?

I have reviewed protocols involving pediatric research where investigators and IRBs have classified the research as minimal risk, no direct benefit, and clearly it is greater than minimal risk and no prospect of direct benefit and it could not qualify under 406. They do not understand Subpart

D. They are not capable of interpreting Subpart D and they are not given sufficient guidance with regard to the interpretation of Subpart D.

Perhaps you read in the New York Times about the fenfluramine challenge studies at Mt. Sinai. This was a situation where normal kids were given a low monoamine diet. They then underwent a fenfluramine challenge, which is a compound related to Phen/Fen which was taken off the market. Then they underwent serial blood sampling in a hospital.

Now these were normal controls. Obviously, no direct benefit whatsoever. The IRB classified the protocol as minimal risk. I would contend that fasting, hospitalization, low monoamine diet, fenfluramine challenge, serial blood sampling, and exhaustive psychological and educational testing, is clearly more than minimal risk.

So, I mean, that protocol was not approvable under the regulations.

Your comment with regard to research involving children versus adolescents. Well, clearly, as kids develop, they are also developing their autonomy. They become more like adults and less like children. So although Subpart D would certainly apply to adolescents, perhaps it would apply less so than it would to younger children.

DR. SHAPIRO: Yes, Diane?

DR. SCOTT-JONES: For the fenfluramine study that you described, could you say a little bit about what the sample -- what was the sample like and was there parental consent?

DR. PRENTICE: The fenfluramine challenge study that was really problematic was the one that was conducted at Mt. Sinai and CUNY. And it involved ADHD kids with normal controls. And, yes, there was parental consent for both samples.

PROFESSOR CAPRON: Was that the study that involved the siblings of children?

DR. PRENTICE: That was --

PROFESSOR CAPRON: Or was that a separate study?

DR. PRENTICE: That was a second study in a New York Psychiatric Institution. That involved -- they were not ADHD kids. They were kids who were adjudicated as delinquents.

PROFESSOR CAPRON: I thought they were the siblings who were put at risk because of having a sibling who had been adjudicated.

DR. PRENTICE: Correct. That is correct.

DR. SHAPIRO: Diane?

DR. SCOTT-JONES: And were they also African American and Puerto Rican?

DR. PRENTICE: Yes.

DR. SHAPIRO: Eric?

DR. MESLIN: Dr. Prentice, I really enjoyed reading your paper and staff will give you some further comments.

I was wondering, in your presentation you described the process of risk analysis, including identification, and then quantification. But it was not until your recommendations, that you talked about the acceptability of risk and the judgments that IRBs are struggling with, with determining levels of risk and what constitutes acceptable and unacceptable -- while referring to the regulations is admittedly a very difficult place to go, I wonder if you could say a bit about how your IRB struggles with the more subjective nature of assessing the acceptability of a particular level of risk prior to balancing that with some description of benefit?

DR. PRENTICE: Let me preface my response to your question by indicating that, in most cases, a risk benefit analysis is not problematic. There is not a big issue or a big question about whether or not the research is approvable. You probably spend a little bit more time on subject selection criteria and the informed consent process than you do on the risk/benefit assessment but sometimes it is very, very problematic and, you know, we have had protocols that have been tabled three times. It has taken four months before they finally get approved

because of a risk/benefit assessment issue.

And the only thing I can tell you is that good people, who sit on IRBs, struggle with these issues. They bring to the table their own individual knowledge and expertise and moral values and judgments. We encourage them to apply this reasonable volunteer standard and place themselves in a position of the subject. Would they participate in this particular research? Would they accept the risks? And those are the kinds of discussions that would go on, on our IRB, for problematic risk/benefit issues.

Ultimately, it becomes a decision that has to be made by the IRB. Now, relative to that decision, I would like to say that we require a two-thirds majority on our IRB to pass a protocol. The regulations only require a simple majority. I would contend that, if you approve a protocol based upon a simple majority, there is something wrong with that protocol.

DR. SHAPIRO: Alex?

PROFESSOR CAPRON: You have at several points described protocols being approved that you found problematic or actually an outright departure from the intention of the regulations. I wondered what the experience and process you have of knowing about the operations of other IRBs. Is this as

someone who -- in other words, from your testimony, besides talking about the University of Nebraska, are you drawing on experience -- extensive experience in reviewing other IRBs' work as a consultant or a person who is called in as a peer to evaluate them?

DR. PRENTICE: I have been fortunate to serve as a frequent site visitor on OPRR for cause compliance site visits so I have had an opportunity to review, you know, a lot of IRBs and a lot of problematic cases that precipitated the for cause visit in the first place.

I have also been fortunate to be asked to be a consultant to review IRBs across the country. So from that perspective, I have gained a lot of experience, but relative to the problems that we have encountered in reviewing our own protocols, there was one particular protocol involving the administration of growth hormone to children with Turner Syndrome.

We felt that protocol was unapprovable because it involved a placebo control which basically meant that kids with Turner Syndrome were going to get injected three times a week with saline for three years. We felt very strongly that that protocol was not approvable under the regulations and it was also not ethical.

We turned it down. We received a great deal of pressure from the investigator and from the drug company who literally wrote me a letter and basically said, "Well, yes, the placebo controls will get benefit because the injection of a placebo is a stressor and stressors are known to precipitate growth hormone secretion, therefore the kids are going to grow." I mean that was absolutely ludicrous.

So we turned it down. A lot of other IRBs turned it down but I also found out that a significant number of additional IRBs actually approved the protocol, including ultimately the NIH, who -- Jeremy Rifkin filed a petition to halt growth hormone trials at NIH. Perhaps you remember that.

And the entire issue of placebo controls in growth hormone studies was analyzed by a NIH panel and they came to the opposite conclusion of our IRB.

We happen to disagree with the NIH's conclusion.

That is one example. Other examples are we encounter a protocol that has got problems. We find out what other centers are involved and I know all the people that are involved, so I call them up and I say, "Okay. I will call UCLA." And I will say, "What did you do with this protocol? Did you have any problems? Did you approve it? Did you consider

this particular concern or that particular concern?" So we engage in a dialogue. I am not suggesting we do this all the time but we do this occasionally.

I would like to see more of that done.

DR. SHAPIRO: Thank you. Other questions from commissioners?

Let me ask -- I have two questions in my mind. One of which you just mentioned as an aside. It sounds to me, from the presentatio,n that at the University of Nebraska where you are, you have really a very thoughtful IRB working very carefully and diligently on all these issues, which is wonderful to hear.

I am wondering about how you would characterize the relationship between the IRB, which you are a co-chair, and the investigators. Is this one where investigators are glad and happy and enthusiastic about the help that you offer on one side or is it otherwise?

DR. PRENTICE: It is probably all over the place. There are some investigators who love us, appreciate us. And there are other investigators who take my name in vain every day.

I believe that IRBs are really in partnership with investigators. I do not believe that we should assume a police role. I do believe that we should assume a partnership role in that we

first ask the investigators to make the ethical decisions with regard to how best to protect the rights and welfare of human subjects by asking the right questions.

You get the information, you review the information, you obtain the necessary clarifications, and if you are satisfied, you approve the protocol. So what you are doing is, you are signing on to that protocol. You are sharing the responsibility with the investigator. So that is the message that I try to get across to our investigators. We are sharing the responsibility with you.

For the most part, our investigators are responsive to that but there are some who are never going to be responsive. They are cowboys and they need to be controlled and that is just the way it is. Those kinds of individuals exist everywhere.

DR. SHAPIRO: Let me ask your judgment on another issue which is -- again it may not be central but it is a language issue which has at least puzzled me some.

As you pointed out in your recommendation there is lots of language around that either asks us to minimize risk, maximize benefits, and as you clearly understand through your presentation, that this is not a simple matter because you are not

simply minimizing risk or not simply maximizing benefits. You are doing something which is looking at both of these things together.

I am wondering whether you think it might be useful to try to search for language which asks investigators to minimize risks in some sense subject to certain boundary conditions, that is that the experiment can go ahead, that there cannot be more than maximum amount of risk, rather than just always talking about minimizing risk by itself, which seems to me not really quite to the point.

But maybe I have either misstated this or have not been carefully -- have not thoughtfully considered this.

DR. PRENTICE: Well, I think that there is one thing I did not point out in my presentation, which I think is appropriately emphasized in the paper, and that is, in clinical research when you perform a risk/benefit assessment, you have also got to consider the alternatives available to the subject in terms of standard therapy.

We ask our investigators, when they submit what we refer to as an IRB application, to perform a risk/benefit assessment of the research compared to the risks and benefits associated with standard therapies available to the subject in a nonresearch context.

So we think that is a very, very important component of a risk/benefit analysis because, if there is standard therapy available to the prospective subject that offers a more favorable potential outcome, then really it is unethical to approve that particular research and we spent a great deal of time talking about, well, all right, what are the risks, what are the benefits of the research versus what are the risks and what are the benefits of the known standard therapy.

You know, I do not have an answer that is really specific to what you are trying to address in the question, because there is no magic formula that we can utilize to figure out how to do this properly. It is just a judgment call and I think that if IRBs approach this from a very, very conscientious perspective, and if investigators do the same, and we work together, then hopefully we will make the correct decision most of the time, but not all of the time.

I can tell you now we have approved protocols in the past that we would never approve now, never. We know more now than we did in the past.

DR. SHAPIRO: Thank you. Bernie, and then Carol.

DR. LO: I want to ask you a question that

draws on what is, obviously, your very extensive experience with other IRBs. There has been a lot of criticism about whether IRBs are doing a good job with their task of protecting human subjects and a proposal has been made in many quarters to certify IRBs or IRB members.

Can you give us a rough idea if IRBs had to pass a reasonable certification test today what percentage of IRBs, in your view, would pass the first time around?

DR. PRENTICE: That is an interesting question. First of all, nobody knows how many IRBs there are in this country. 3,000, 4,000, 5,000. I do not think anybody has a handle on that. Not even FDA. They do not know.

I think that -- first of all, let me talk about accreditation. As you know, PRIMR is developing accreditation standards for IRBs. I think that is very, very important.

Institutions respond to an accreditation stick. You know, if the Joint Commission is going to come in and accredit our hospital and we have to spend a million dollars to get ready, there is no question we spend the million. All right.

If ALAC is going to come in and accredit our animal program and I go to the chancellor and I say, "Look, you know, we need $100,000 to renovate

our animal facilities," the money is there immediately. If I go and ask my chancellor, "I need two more IRB staff because they are overworked, they are overloaded, and we are very concerned about doing the job we need to do," the response is not positive. It is more positive than it used to be, considering the events in the last two years, but it is still not as positive as it should be.

So I think accreditation is very important.

I think certification of IRB administrators is very, very important because back in the 1980's, early 1980's when I started in this business, an IRB administrator was a secretary, that is it. They were paid as a secretary, viewed as a secretary. That is not the case. IRB administrators are professionals. They need to be recognized as professionals, paid as professionals and certified as professionals. That is an ongoing process that ARENA and PRIMR have initiated beginning next October in San Diego. So I think that is going to be a great boon to ensuring adequate protection of human subjects.

I do not think that you need to certify IRB members. That is probably going beyond the pale but I do think that IRB members need to be trained.

When I go out on site visits, we ask questions of IRB members. They do not understand

the regulations. They do not know what Subpart D is. I have asked pediatricians, who are the representatives of children on IRBs, "How do you review a protocol involving children? How do you apply Subpart D?" Well, they do not know what Subpart D is.

When you explain the categories, they do not know what those are.

Now I am not suggesting that that is universal but I am suggesting it is a significant gap in knowledge. That is now being corrected by mandatory training enacted by NIH as of October 2nd, which I think is great. That is what we ought to have. Mandatory training of all investigators.

Probably the best way to protect human subjects is to ensure that investigators are not only trained, but they are also, more importantly, sensitized to their absolute obligations.

DR. SHAPIRO: Thank you.

Carol?

DR. GREIDER: In some of the material that I have been reading over the past few months, it has become clear that, in addition to protecting human subjects, that there is a certain amount of pressure that IRBs may feel to protect the institution in some, perhaps, legal sort of way.

Do you have any comment about whether that

is common or any other comments?

DR. PRENTICE: Well, first of all, the -- it is not the charge of the IRB to protect the institution from liability. However, most IRBs are at least cognizant of legal liabilities associated with certain kinds of protocols, and I do not disagree with them being cognizant.

However, I do not think that should be the primary focus of their review. If they have some concerns, they ought to refer their concerns to legal counsel.

Certainly we are seeing an increase in the litigation relative to clinical research. I have been fortunate to have served as an expert witness for a number of universities who have been sued for medical malpractice in clinical research cases, that had regulatory compliance considerations. So in other words, the IRB was named in the complaint.

I think we are going to see more of that, as time goes on, so I think IRBs need to be cognizant of the fact that, if they perform a thorough complete review according to the regulations, document everything, that is probably providing additional legal protection for the institution, and I do not disagree with doing that. I do, however, disagree with the mountain of paperwork that we are faced with. By dotting every

I and crossing every T, it is absolutely enormous. It takes a great deal of time.

DR. SHAPIRO: Larry?

DR. MIIKE: You mentioned in your prepared talk "ongoing monitoring." From what we have heard, that hardly ever goes on, through no fault of anybody's. Just including -- just not the capacity to do it. And the information that is provided is often useless, in the sense that you get a report on adverse events, but there is no context in the sense that is that a rare thing or is that common. Can you comment about that?

DR. PRENTICE: IRBs are supposed to perform ongoing monitoring and probably the most important aspect of ongoing monitoring is to ensure that the risks and benefits of the research remain acceptable. And the occurrence of unexpected adverse events can influence a risk/benefit relationship of the research clearly.

There are two kinds of adverse events. There are those that occur within the institution itself. I think that IRBs have to pay particular attention to those kinds of adverse events because they have got to be responsible for their own research subjects. And those are not problematic for most IRBs.

What is problematic is the number of

external adverse events or IND safety reports that IRBs get. We are getting about close to 3,000 external adverse event reports per year. UCLA is getting around 6,000. Minnesota, I know, gets more than we do. And IRBs are supposed to look at every one of these adverse event reports. And we get adverse event reports that are related, or unrelated, or of unknown relationship to the research, that are serious, not serious, expected, unexpected.

What are we supposed to do with this? There is no denominator. Okay. There is no numerator. We have no data to evaluate that. IRBs cannot act as DSMBs. We have got to change that system.

We use a triage approach to adverse events that come in from the outside. If they are not serious and related, or possibly related and unexpected, we do not review them. But those that meet that category, we ask the investigator to perform a rather lengthy analysis to the best of his or her ability, give this to the IRB, it is prescreened by an IRB events -- or an adverse event subcommittee, and then it is sent to the full IRB for their consideration. That way we can triage the number down to an almost manageable level but we still recognize the fact that we still do not have enough data to be, you know, looking at these.

I really think the DSMBs ought to be given IRBs summary reports when they have analyzed aggregate data. Give it to us. Tell us what you think and then let us act. Do not expect us to act on every single individual adverse event. That is not productive.

DR. SHAPIRO: Thank you. Any other comments?

Well, let me thank you very much, not only for the paper, but for coming here today. Please give our thanks, also, to your colleague, Professor Gordon, on this. We really very much appreciate the effort. Thank you very much for coming.

DR. PRENTICE: Thank you very much.

DR. SHAPIRO: Steve, do you have a final question?

MR. HOLTZMAN: Can we get a copy of the slides?

DR. PRENTICE: Sure. You want a copy of the slides?

MR. HOLTZMAN: Yes, that would be fabulous.

DR. SHAPIRO: If you could just give it to a member of the staff, we could reproduce it.

DR. PRENTICE: Sure, they are all on PowerPoint with the exception of the couple. I can give you that personally if you want.

DR. SHAPIRO: Okay. Thank you. Thank you

very, very much for being here today.

We now want to move directly into our next panel.

Marjorie?

PANEL V: PERSPECTIVES OF OVERSIGHT SYSTEM FROM IRBs

DR. SPEERS: As our next panel is assembling themselves at the table, let me just give a few brief remarks.

We are moving into the two final panels for today. Both of these panels have been asked to address the same issues from their unique perspectives.

This first panel is composed of individuals who are IRB administrators, institutional officials, or IRB chairs. And in the case of a couple of them, they have served maybe previously as an IRB chair, although, currently they may be an IRB administrator.

They will be discussing issues, therefore, related to or from the perspective of the IRB or the institution.

Then we will have a panel after lunch that will be discussing issues from the researcher's perspective where we have several researchers who will be talking about the same issues.

What I asked each of the panelists to do

was, to begin by giving a few prepared remarks where they would highlight some of the major concerns that they see with the federal oversight system, not all concerns, but to choose what they considered to be major concerns, and also to comment on potential solutions and recommendations for us.

So now that everyone is assembled, let me introduce them.

We have Mr. Daniel Nelson, who is director of the Human Research Studies and Associate Professor of Social Medicine and Pediatrics at the University of North Carolina-Chapel Hill.

Ms. Moira Keane, who is the director of Research Subjects' Protection at the University of Minnesota Health Center.

Dr. Ray Stinson, the Assistant Vice President for Research at Wayne State University.

And Dr. Robert Nelson, who is Assistant Professor of Anesthesia and Pediatrics, and director of Research Regulatory Affairs Office at the Children's Hospital of Philadelphia.

Thank you and welcome.

Generally we just sort of start in the order of which you are on the agenda and so we will do that today and start with Mr. Nelson.

DANIEL K. NELSON, M.S.

DIRECTOR, HUMAN RESEARCH STUDIES,

AND ASSOCIATE PROFESSOR OF SOCIAL MEDICINE AND PEDIATRICS
SCHOOL OF MEDICINE
UNIVERSITY OF NORTH CAROLINA-CHAPEL HILL

MR. NELSON: Thank you for the opportunity to speak to you today. Given just these few minutes to provide our IRB perspectives, I figure I can either cover a very few issues in some depth or get a broad range of issues out on the table, and I opted for the latter, recognizing that you are receiving complete papers on some of these single topics. So I will move fast and be happy to provide details during the discussion.

(Slide.)

There is a transparency up there that should match. There are two pages that, hopefully, you now have in hand.

Let me start with issues that have been around for a while.

When I was invited to present here today, I asked some colleagues what they thought the NBAC should hear, and several of them gave me the top quote or something along those lines. "The common rule is a nice idea...but it is, unfortunately, not reality."

There are overlapping, contradictory regulations that lead to catch-22s and nonsequitors,

the FDA pointing us in one direction, the HHS in another. There are some IRBs that only need to worry about FDA regulations, others that work strictly from HSS regulations.

Those of us, at institutions with diverse research portfolios, end up trying to serve several masters and many of us have promised, via the assurance mechanism, to apply HHS regs across the board regardless of funding.

So we are left doing mental gymnastics that really have little to do with protecting human subjects. It is difficult to argue, I think, that subjects receiving a drug in an industry sponsored study deserve more or less protection, than subjects receiving perhaps the same drug in an NIH sponsored protocol.

Even more disconcerting are loopholes that allow some research in some settings to occur without any kind of IRB oversight or informed consent regulations. I believe the DeGette-Waxman-Mica bill that is now moving through Congress would be a positive step toward bringing consistency and closing some of these loopholes.

Variability is widespread. If the regulatory discrepancies I have just mentioned are not enough, the regs themselves are vague enough, that two reasonable people can come up with

differing interpretations, and we have many more than two people, and not all of them are reasonable.

Some of this is simply the nature of the beast, with as many people and as many institutions and as many studies as we have trying to apply and interpret, but some of it relates to the lack of standards and the difference in abilities and resources. Clearly not all IRBs are created equal.

There are now several initiatives to start to bring some level of standardization. I have been involved, and have been fortunate to be involved at the national level, with the ongoing initiatives out of ARENA and PRIMR to establish accreditation of institutions and certification of individuals. I would be happy to discuss that later.

Conflict of interest has also been around for a long time. It is inherent to the process. I think I should have struck the word "clinical" there. It is inherent to research in general. It is also a nature of the beast sort of scenario.

Certainly any time a physician enrolls a patient into a trial, there is a built in inherent conflict of interest, and the increasingly large amounts of money only add additional -- another layer of conflict.

There are questions regarding disclosure, whether to institutions, to IRBs, to patients, and

there are questions regarding institutional handling of funds from clinical trials. Clinical trials more and more are being conducted in nontraditional settings, where the physician serves as an investigator, serves as institution, and what I mean by that is, increasingly there is no institution, so it becomes somewhat meaningless to talk about institutional management of the conflict of interest because the physician and the investigator and the institution may be one.

Therapeutic misconception. I know from your materials and from the discussion yesterday that you already have a good feel for this and have spent time discussing it so I will not waste time today or insult you by defining it further. Just let me say that we at UNC, Larry Churchill and Nancy King and I and others in our department spend a great deal of time thinking about this. We recognize it as a problem and I do not think they would forgive me if I did not, at least, list it as something IRBs should be concerned with. There are ample opportunities in this research process for the blurring of obligations and for the blurring of expectations.

Pre-IRB scientific review. There are those that argue that review of the science is not our job. It is certainly not our primary reason for

existence, but solid science is integral to that risk/benefit calculus that you just heard about from Ernie Prentice.

Ethicists, perhaps some of you around this table, are fond of saying that "Bad science is unethical science." Here, too, there is variability in the type and depth of review that occurs. The IRB is admittedly not constructed as a merit review panel but far too often we are serving as the only body other than the investigator or the sponsor to examine the study design and other issues.

Compensation for research related injury has been around for a while. Just let me say that this is an area where our ethical obilgations to do right, by the people who volunteer their time and their bodies, seems to be in conflict with institutional policies and with the regulatory requirements that currently exist.

IRB as default. I have listed two examples there of clinical scenarios and these truly are clinical scenarios where, one physician may be acting in the best interest of one patient, with no intent to gather data to conduct research, but there is really nobody else around to oversee this process and so, just because there is no one else, the IRB gets handed this task and often gets placed in a tenuous position with little effect.

There are impaired lines of communication -- several questions were raised during the previous session -- between the IRB and regulatory agencies, between the IRB, and here I mean the local site IRB, and other IRBs reviewing the same study, between the federal RAC as, just an example of another external body from which we could benefit, and from DSMBs who are in a much better position to do what IRBs are very poorly equipped to do.

And that is to deal with adverse event reporting. It has already been discussed.

(Slide.)

I think the fastest way to summarize this, from my perspective, is to leave you with this mental picture.

You do not have a copy of this but this portrays the ancient Indian parable of the six blind men who set out to describe the elephant, and depending on which part of the elephant they feel, they get a much different picture. Of course, the one feeling the tail describes a rope; the one feeling the leg describes a tree and so on.

In this picture, the elephant in my mind, represents the aggregate global adverse event experience across a clinical trial, and I would suggest that local IRBs are just about as well equipped as these six blind men of India, in having

a realistic picture of what is going with the trial as a whole and, in fact, beyond simply adverse event reporting. I think this analogy could be drawn across the clinical trial interplays which now takes place across many more sites than the regulations initially anticipated.

(Slide.)

These are evolving issues. I would just note that this is a much shorter list and my point here is that these problems did not start with Duke. They did not start with Jesse Gelsinger despite the media's rather recent discovery of the IRB world. Most of these issues have been around for a long time and we have been grappling with them for a long time.

Growing workloads. I guess this is an old issue but increasingly an evolving issue. I had a graph along that I will not show in the interest of time showing our local volume but just suffice to say that our volume and that of institutions around the country are going up and up and up with no end in sight. That is a positive reflection of the amount of work being conducted but grappling with that we are now up to four boards just with our biomedical oversight meeting once a week to handle the volume that we have at UNC.

The complexity is also increasing. New

technology is bringing new challenges and you are very familiar with those.

Evolution of the clinical trials enterprise. I have mentioned some of that. More and more research is migrating out of the academic medical centers, the traditional setting, into nontraditional settings, and so we have a multicenter world into which we are trying to impose single site regulations that were developed for a much different time.

I am in favor of some efforts to be more innovative and imaginative in centralizing review but how do we do that without losing the local perspective? And here I would just like to mention that when we discuss this commonly, the focus is on sensitivity to community norms, community standards with an eye towards the subjects.

And clearly that is very important but something that is often overlooked and I think perhaps just as important in overseeing this process is a feel for the capabilities and perhaps the proclivities of our local investigators. I can guarantee you that I have a much better feel for what our investigators are up to than a central IRB across the country could ever be by reviewing the medical license and the CV, which is about the extent of interaction with the investigators

conducting a study.

Evolution of IRB work as a profession. As you just heard, running IRBs is something that has evolved from a process that was dumped on a personal secretary of whoever happened to be dumb enough to take the chair a few years ago, to then becoming part of an administrator's job, to then all of an administrator's job, to now really a profession with a career with faculty level appointments at some institutions, our's included, following nationwide searches. Some of us at this table are now getting calls from professional head hunters like might go after CEOs, which is perhaps not inappropriate with budgets in this area growing over a million dollars in some institutions, with large staffs to manage, and large responsibilities considering that the work may influence the subjects' lives and well being, not to mention several hundred million dollars of grant funding, which is important at the institutional level.

Mandates without standards and without resources. The mandates that are coming out are good. They are needed but we have very little guidance on how to actually apply them, what is expected, and even less resources. The unfunded mandate is the fear of IRBs across the country.

Let me finally combine the last two in the

interest of time. A shifting emphasis from protection to compliance and yet another report. In the last two years there have been eight to ten reports and you are working on another one, and I encourage you to complete that task, and an equal number of very public shut downs.

It is now to the point when I give a talk I can usually pick up the morning newspaper and have it as a prop to use during the talk so I was not surprised but I also was not happy on the plane yesterday to grab the USA Today and the front page headlines read "Clinical Trials Halted, Feds Say that Cancer Study Endangered Patients," and another institution has been shut down.

Now I should hasten to point out that I agree with the findings of many of these reports, most of them accurately describe the system. I agree with the need to probably go out and shut down some of these institutions not only to correct problems at that site but to get the attention of the rest of the world, which has certainly been occurring.

However, I think we need to remember that compliance is simply a means to the end. The important end is the protection of subjects and it is something we are in danger of overlooking as we worry -- as institutions are scrambling to dot the

I's and cross the T's.

Thanks for your attention.

DR. SHAPIRO: Thank you very much. I think if there are any clarifying questions we could take them now. If not, I would ask people to hold their questions until everyone has made a presentation.

Any clarifying questions?

Okay. Let's move on. I believe, Ms. Keane, you are next.

MOIRA A. KEANE, M.A.,
DIRECTOR, RESEARCH SUBJECTS' PROTECTION PROGRAM
IRB/IACUC, UNIVERSITY OF MINNESOTA HEALTH CENTER

MS. KEANE: Thank you.

I am going to, I think, reflect some of the comments that Dan has made and I think that you will see a common theme as we approach some of the issues and concerns because we are seeing a kind of nationalization or globalization, if you will, of some of the issues facing IRBs.

We are operating right now under a climate of distrust. And I am going to focus my comments on four sections. Competing expectations, conflicting commitments, culture change that is necessary and communication.

First of all -- and I am not going to belabor it. The climate of distrust is well known to this group. Congress does not trust the

agencies. The agencies do not trust IRBs. Investigators are not trusting IRBs. And foremost in our minds should be the fact that the public is also distrusting the system. They are very concerned that there is not an infrastructure in place to protect their interests in the research participation.

It is critical for us to restore that trust and I am hopeful that the report that comes from this group will help move that trust along.

First of all, with competing expectations. IRBs are charged with assuring that plans are in place for protecting the rights and welfare of subjects. This is distinct from assuring that the subjects are protected during the course of the research project but IRBs are being held accountable for that protection.

The actual protection occurs at the bedside. It is the responsibility of the researcher who is present during the course of the research.

Our focus for reform should include the researcher role in this constellation so we should not just focus on the IRB staff or on the IRB membership. Now that should not diminish the role that the IRB should play but we need to be sure that we are focusing on the researcher.

Further competing expectations: We have

had a focus on accountability and documentation rather than on the responsibility and the verification component. I think Ernie alluded to this earlier when he mentioned monitoring as an essential component. There is tremendous competition between research goals and economic incentives that have changed the altruistic goal of research as a benefit to humankind into research as a source of profit for institutions, researchers and sponsors.

This has led to imposition of escalating agency expectations, imposing unfunded and often burdensome mandates for IRBs with little regard for the measurement of whether the new mandates actually add to the enhancement of protection.

I would cite an example here of the assurance process. The multiple project assurance and the Byzantine system of single project assurances are a hindrance to most IRBs and do not, in fact, I believe add much measure of protection for the individuals who are participating in the research projects.

Institutions expect that a system of volunteers with meager staff are knowledgeable and ever vigilant when, in fact, there are significant disincentives for IRB service at most institutions.

Researcher perceptions of IRBs focus on the

speed and the need for ease of IRB review rather than on the value of enhancing protection as a product of the review.

There are conflicting commitments. The resource commitment at all levels in the IRB system is woefully inadequate to the task. Federal agency support has been deficient so that they cannot provide the necessary guidance and education that IRBs need.

The recent new initiatives for education of IRB members and staff are noble and necessary but there is a danger that in an effort to comply with this requirement, especially given the time limits imposed, institutions will foster inadequate educational initiatives, which may do little to improve the knowledge of regulations and responsibilities and may, in fact, delude us into a sense of complacency and comfort with our knowledge and understanding of what is necessary to protect human subjects.

There are tensions between financial pressures to attract lucrative research contracts to institutions, which fosters an atmosphere where short cuts and questionable alliances divert our attention from the rules and regulations.

The perceived blurring of lines between research experiments and therapeutic interventions

needs distinctions both for IRBs and for our public education.

We need a culture change. The federal agencies must change. Oversight by the agency personnel should be constructive and corrective, and punitive action should be limited only to severe cases of noncompliance.

I say that at the same time I think the pressure has to continue. We have to hold institutional officials to the public commitments and assurances that they have made. Without that pressure we will not have the reform that is necessary.

Institutional supports must be bolstered to shift our thinking from the volunteer role of IRB service to a full functioning, educated and professional support system.

Institutions must stop paying lip service to supporting the IRB function and actually in spirit and fact support IRB members and IRB staff.

The focus on medical research both from this group and, unfortunately, in most of our home institutions is really a detriment to participants in behavioral research projects. The attendant risks in behavioral and social sciences may be harder to measure but they have far reaching and often lasting effects on participants.

The biomedical model that we have superimposed over the behavioral research is insufficient to the task of assessing risk in these kinds of research projects and we must have reform in those areas.

I want to talk a little bit about communication. We have mixed messages from the agencies. They are tough but they do not have teeth. They have teeth but they cannot help us.

We cannot have it both ways. IRBs are reluctant to go to the agencies that are there to help guide them for fear of sanction. We are reluctant to pick up the phone and call the federal agencies and ask for their advice on research projects for fear that it will raise a red flag and attract undue attention to a process in our institution that may not be deficient but may appear to be based on an innocent phone call or query.

There is tremendous pressure to have IRBs move quickly through the approval process, particularly for lucrative clinical trials. The financial pressures are tremendous. Much as we try to insulate our IRBs from the knowledge of budgetary constraints might be in place on a particular research project, the pressure is there.

We need to work towards a new system that supports researchers and supports a system of

validation and verification that, in fact, human subjects are being protected.

The rules and guidance generated in the middle of the past Century are not sufficient to deal with the challenges of current research initiatives. There are very few simple clinical trials anymore.

On my desk right now we probably have two or three very large program project grants that have been submitted to the federal agencies for funding that involve human research, animal research, gene transfer, biosafety issues, the whole gamut.

There is a very complex matrix of regulations and requirements to follow those projects through to safe completion. These are different kinds of challenges than what we faced even ten years ago.

Now I have really painted a fairly bleak picture of IRBs and I do not want to leave you with that. I believe that there is a tremendous amount of hope out there in the IRB community. With any kind of crisis we have an opportunity. We have an opportunity to assess what is working, eliminate ineffective practices, and enhance effective programs.

I would strongly urge that we have agency refocusing to guide and correct as a means of

reform. We need to critically examine the practices that enhance protection and diminish those that add burden.

I hope that the agencies will reach out and communicate with the field. The suggestion that we include a citizen IRB advisory component to federal agency oversight is long overdue.

The distrust and negative reports are not the entire picture.

Headlines -- you know, institution in full compliance with all research regulation is unlikely to make the USA Today headline that we could use as an example. That is unfortunate. The media is looking for the sensational story. That is not helping our public trust our system.

But just as with any prevention program it is hard to measure and account for our successes. It is difficult for IRBs to demonstrate precisely how and when we have protected people but I believe that the system of protection is better for having IRBs in place than we would be if we went without a system of oversight at the local level.

I am also pleased to say that I think that IRB staff and members whom I have had the pleasure of encountering in my work both locally and nationally are some of the most dedicated altruistic people that I have encountered in my professional

work. They truly believe that their work has an impact on protecting subjects and that they can make a difference.

But we need your help to continue that. We need your help to continue what works, eliminate our wasteful practices, and enhance the protection of the true heroes in this process, and those are the human participants in our research projects.

Thank you.

DR. SHAPIRO: Once again let me see if there are any clarifying questions. We will come to more general questions later on.

Yes, Alex?

PROFESSOR CAPRON: Could you give us an example of the kind of inquiry to a federal office that would trigger a sense of deficiency where there was not one present?

MS. KEANE: Yes. I think that especially in areas of noncompliance where an IRB is questioning what should we do if we find out that a researcher has proceeded with a project without submitting it to the IRB or a researcher has deviated in a significant way from the approved protocol, how should we handle that. That is not a naive or infrequent question.

And the fact that I would raise the specter of noncompliance at an institutional level by

calling a federal agency and asking that question is something that does cripple IRB staff and chairs from proceeding.

So we often turn to our colleagues for consultation, which for the most part can be very beneficial but it could, in fact, get us in trouble if we consult with the wrong colleagues.

DR. SHAPIRO: Thank you. Any other clarifying questions?

Okay. Dr. Stinson?

E. RAY STINSON, Ph.D.

ASSISTANT VICE PRESIDENT FOR RESEARCH

WAYNE STATE UNIVERSITY

DR. STINSON: I am the Assistant Vice President for Research at Wayne State University where I am responsible for research administration and the institution of research compliance programs. Among others, these include the Human Investigation Committee and the four IRBs at my institution.

The administrative staff of 7.5 people and the chairs of the four IRBs and the Human Investigation Committee chair, all faculty members report to me for their IRB related activities.

Each of the IRBs consist of approximately 15 to 20 individuals with two to three community representatives on each committee. Consequently, approximately 80 people are members of the IRB at

Wayne State. More than 1,800 protocols are active at any one point in time.

Wayne State is an urban Carnegie One research institution with approximately 32,000 students. In fiscal year '99 we conducted more than $200 million in research funding, approximately 40 percent of which involved the use of human subjects as part of the research methodology.

We conduct research under an MPA that includes all research activities at Wayne State, eight hospitals within the Detroit Medical Center, and the John Dingle VA hospital. The Detroit Medical Center has approximately 3,000 beds and the Wayne State University Program for Human Research Protection covers all of their research activities.

Before I make my comments, I would like to thank you for allowing me to discuss institutional concerns regarding the protections of human subjects. I would like to emphasizes that I will be addressing the issue from an institutional perspective and not specifically from an IRB. However, I do hope that these two perspectives are compatible.

At Wayne State, we believe that the four IRBs are there for the protection of human subjects and not for the protection of the institution. As such, many of the activities related to human

subjects protection are the responsibilities of the institution and not the IRB. For example, these include our educational programs for faculty and research staff, maintenance of our MPA, institutional review of selected research protocols, and compliance with institutional, state and federal policy.

In working with the faculty, research staff, and specifically members of the IRB, I constantly emphasize that we live or die by compliance with our MPA, not the Common Rule.

While the assurance states that we will conduct research in compliance with 45 CFR 46, it also assures that we are in compliance with 21 CFR Parts 50 and 56, state laws, and institutional policies regarding human research protections. While they and you may think that there is little difference, I believe that it is critical that we remember and regularly acknowledge that our institutional policies go way beyond the requirement of the Common Rule.

While it is important for institutions to voluntary extend the policies and procedures to include all subjects in order to maintain credibility with the public and to maintain our adherence with the principles established in various international codes, many institutions have not

understood the financial cost of this extension.

Quite often, institutions have used adequate financial resources associated with staying in compliance with the Common Rule,i.e. funds available from indirect costs under A-21, and attempting to stretch them to provide for the protection of all research subjects. This has led to problems in the belief that academic institutions are not providing adequate financial resources.

It is my contention that academic institutions are providing adequate financial resources for extending the principles of the Common Rule. However, many of them are not providing adequate financial resources for extending these principles of other Common Rule to all human research being conducted at their institutions. Understanding and communicating the importance of this extension and the financial costs associated with the institutional decision is a major flaw of many institutional programs.

For the remainder of my discussion I would like to emphasize how research, particularly clinical research, has changed since 45 CFR 46 were propagated.

This change in how we conduct clinical research has made it difficult for academic institutions to stay in compliance with their MPA.

I believe that these can be grouped into five categories. The difficulties in identifying the institution, the difficulties in identifying the researchers, the difficulties in identifying what is research, the difficulties in identifying the research subjects, and finally the difficulties in identifying the community.

While the commission has spent time in discussing the difficulties in identifying what is research and in identifying the research subjects, specifically as it relates to genetics, I would like to spend my time discussing how difficult it is to identify the institution and the researchers in a research protocol. If time allows, I will discuss the problems in identifying the community in which the research is conducted.

Unlike when 45 CFR 46 was originally propagated, institutions as defined by the Common Rule are really multiple institutions with shared goals that are acting as a single research organization. For example, the Wayne State MPA covers all behavioral and health related research for ten separate institutions located within Southeast Michigan. While this integrated approach is advantageous to health care delivery, the administrative cost related to maintaining a program for human research protection is substantial. In

fact, it is a constant struggle for the Office of the Vice President for Research to even be aware of new affiliations proposed by affiliated institutions that may have an effect upon our MPA.

The research paradigm used when 45 CFR 46 was developed included research conducted by one investigator, at one institution, and in one community. Over the years, we have manipulated the regulations to accommodate the effects of conducting research at one institution and in one community to clinical research conducted by many investigators at numerous institutions and in multiple locations.

However, collectively, we are not efficient because this duplication of this effort is that the cannot -- I am sorry. However, collectively, we are not efficient because many of the other communities throughout the country duplicate the work of our committee.

The effects of this duplication of effort is that institutions cannot or will not prioritize when approval and oversight is unique to them and when it can be shared with another IRB.

In addition, the complexity required to maintain our compliance with the Common Rule makes it easy for investigators and institutions to violate institution policy without deliberate intent. I will defer to my colleagues to identify

the problems with adverse event reporting, languages in the consent form, and other areas in which multicenter studies have affected how clinical research is reviewed and approved by the local IRB.

If requested, I would be willing to provide additional examples.

This use of multicenter studies is really a way of decentralizing the research activities. I would like to describe what I believe is the next wave in this decentralizing approach to conducting clinical research. These new approaches will make it even more difficult to define the institution and research staff responsible for conducting clinical research under an MPA.

As part of the diagnostic related group's mechanism for reimbursing academic health centers, research groups are establishing research affiliation agreements with individual physicians, practice plans and health care institutions that have traditionally not been involved in the research enterprise.

Each of these relationships individually can be handled under the current Common Rule. For example, we could use a single project assurance for independent investigators, the interinstitutional agreements and other agreements provided by OPRR to extend the definition of the institution and the

research staff covered by the MPA.

However, in the past these have generally been protocol specific. As part of the disclosure to the IRB, the investigative team would identify researchers and other institutions that may not be covered by the MPA. The IRBs would alert the institution and additional agreements were signed to allow the research to be conducted under the MPA.

Even in today's environment it is often difficult to remain in compliance because of the various types of agreements that may be necessary and when they need to be applied. Many of these agreements require amendments to our MPA that are time consuming.

In the future, investigators would like to not define who is conducting the research until after a patient has been identified. For example, the investigator would like to treat a patient under a research protocol because of the advantages of participation in the protocol. He/she would like the option to include the local physician or health care provider as a member of the investigative team so that they can conduct simple blood work, x-rays or provide certain chemotherapies at the local level.

Because the patient is not known in advance, the appropriate agreements cannot be

negotiated with the physician and/or his or her institution in a timely fashion so that the patient can be treated on a particular protocol.

While it may make sense from a health care delivery standpoint and it certainly makes sense from a reimbursement perspective, it will be a nightmare and will be extremely expensive for the institution to manage and stay in compliance with the Common Rule.

Our Karmanos Comprehensive Cancer Center is currently negotiating with approximately 50 different groups of individual physicians, practice plans, health maintenance organizations and health care institutions for conducting clinical care and research in this decentralized approach to research.

If successful, I can assure you that it would be extremely difficult for us to remain in compliance with the Common Rule because of the number and different types of agreements that must be negotiated before research that may be part of clinical care is provided to the patient research subject.

DR. SHAPIRO: Thank you very much for those thoughtful remarks. Again, any clarifying questions at this moment?

Dr. Nelson? Thank you.

ROBERT NELSON, M.D., Ph.D.

ASSISTANT PROFESSOR OF ANESTHESIA AND PEDIATRICS
DIRECTOR, RESEARCH REGULATORY AFFAIRS OFFICE,
CHAIR, INSTITUTIONAL REVIEW BOARD,
THE CHILDREN'S HOSPITAL OF PHILADELPHIA

DR. NELSON: Thank you for the opportunity to speak to you this morning about the system of institutional review boards from the perspective of an IRB chair. Although my opinions owe much to conversation with others involved in IRB activities, they are entirely my own. My intent this morning is to provide a more general perspective, yet I will mention some specific areas of concern towards the end of my remarks.

There are two important aspects of my own experience that inform my point of view. First, my mother-in-law is now four years out from the diagnosis of pleural mesothelioma, an asbestos related cancer of the lining of the lung that is usually fatal within one or two years of diagnosis. In 1996, she chose to enter a Phase I trial at the University of Pennsylvania involving the intrapleural instillation of a gancyclovir susceptibility gene using an adenoviral vector, followed by two weeks of the drug gancyclovir. The results were not dramatic, although the growth of the tumor appeared to stabilize.

As her symptoms worsened, in 1988, she

decided to enter another Phase I trial of an angiogenesis inhibitor drug, this time at the University of California, Los Angeles.

In combination with chemotherapy, her symptoms have resolved and her tumors have either diminished or entirely disappeared. I have her permission to tell you that she is very proud of being patient number 14 in the Penn trial and patient number 18 in the UCLA trial.

As you all undoubtedly know, the University of Pennsylvania program is no longer in the business of clinical research. The UCLA program was prominently mentioned in U.S. News and World Report last year in an article critical of the medical research enterprise.

It would be a shame in my opinion if a few high profile deaths of participants in clinical research protocols led both to the false impression that research participants are being seriously injured on a widespread basis or to the slowing of the pace of important clinical research.

Second, I am a practicing pediatrician, who has worked in both neonatal and pediatric intensive care units. Much has been written about the apparent conflict between the roles of researcher and physician, often presenting the simplistic view that a physician acts in the patient's best interest

while the clinical researcher values the successful completion of research over the participant's welfare.

However, physicians as a whole are prone to overestimate the benefit and underestimate the risk of a clinical intervention and to suggest unproven interventions based on biological plausibility in the absence of efficacy -- all in the pursuit of a patient's best interest.

One could speculate that the deaths of research participants at the Universities of Pennsylvania and Rochester were due to the inappropriate extension of these clinical attitudes to the research setting, causing the physician/researchers to press forward in violation of preestablished exclusion criteria or while discounting procedural complications.

If the welfare of participants is not a concern to clinical researchers, how do we explain the contrast between the exceedingly rare death on a research protocol due to researcher mistakes or unanticipated adverse events, and the recent Institute of Medicine estimate of between 50,000 to 90,000 avoidable deaths due to clinical mistakes? Being a research participant appears to safer than being a patient.

Recently I was asked to comment on the

death of an infant that was attributed to the drug Cisapride administered as part of a research protocol. Apparently the consent form was inaccurate as it misleadingly stated that the drug was approved for the study indication, that is, gastroesophageal reflux, while failing to mention that it was not approved in this age group.

To focus on this mistake, however, is to miss the broader context of the indiscriminate or off label clinical use of this medication which has led to a far greater number of deaths. I suspect that very few pediatricians inform parents that this drug is not approved for use in infants and young children.

The inaccurate consent form does undermine the trust of potential research participants for the research process. However, to conclude that research is unsafe when compared to clinical practice is simply false.

I have had the privilege of serving as a consultant to three institutions either before or after they were visited by the OPRR. I believe Ernie was part of one or two of those visits. Two of which resulted in highly visible suspensions of their Multiple Project Assurance.

Although there were important procedural inadequacies that needed to be corrected, I am not

aware of any serious injury or death that resulted from the identified deficiencies in IRB review and ongoing oversight.

In fact, I see no apparent relationship between the performance of IRB review and oversight responsibilities, even if carried out to the letter of the federal regulations, and the possible prevention of the highly publicized deaths that have captured our attention.

Consider with me two questions. First, which of the following IRB activities would have prevented these deaths? Continuing review, review of amendments, review of adverse event, verification of information from sources other than the investigator, auditing, or data monitoring procedures? These are all IRB responsibilities according to the Common Rule.

Second, which of the following recently announced initiatives would prevent these deaths: Civil financial penalties, auditing of the consent/reconsent process, clinical trial monitoring plans for all phases of research, conflict of interest guidelines, or education and training of key personnel?

The real issue is not the IRB review process but how to impact on investigator behavior. In my opinion, the only suggestion that would appear

to have a positive impact is education.

There is no doubt that many IRBs are understaffed and overworked. There is no doubt that many institutions have not provided the necessary administrative infrastructure for the IRB process, instead relying on voluntary time and insufficient administrative support. In my opinion, however, the important work is getting done.

Some committees may cut corners in arguably nonessential areas. For example, full committee review of the progress report of ongoing protocols that present no problematic issues, full committee review of grant applications, as opposed to the protocol contained in the grant, or review of individual off site adverse events.

Each of these examples has a very low yield with regard to the protection of research participants. Although the initial OPRR suspensions were a necessary wake up call for university administrators and highlighted the inadequacy of institutional support for the IRB, later investigations began to focus on procedural requirements that arguably have little impact on the protection of research participants.

Only recently have guidelines allowing for just in time review of NIH grant submissions and the use of Data Safety Monitoring Boards attempted to

reduce the regulatory burden on IRBs.

However, I am concerned that this shift to Data Safety Monitoring Boards is not well thought out, and may undermine the protection of research participants by focusing primarily on whether the data reaches a predetermined level of statistical significance rather than on any information pertinent to the willingness of current participants to continue in the research, which is the charge to an IRB.

Meaningful informed consent occurs through a process of communication that is not reflected in the written document. Most of us agree that the document is neither necessary nor sufficient for adequate voluntary and informed consent.

The IRB could monitor the quality of informed consent but we lack an adequate tool for measuring this quality. Assume for the moment that we have such a tool. If an investigator routinely met a certain threshold reflecting the adequacy of informed consent, would we be willing to waive the requirement of IRB review of future consent forms as long as this threshold continued to be met?

We should begin to shift away from an emphasis on regulatory compliance and IRB process and towards an evaluation of the outcomes of this process and the ethical behavior we are attempting

to influence.

Such a system would allow for meaningful ongoing monitoring in many areas; direct observations of consent and study interventions; assessment of investigator understanding of research participant protections; assessment of participant or surrogate understanding of the research, and so forth.

Research regulations should be data driven. As I listed before, a number of new initiatives have been proposed by the Department of Health and Human Services. How will we measure their effectiveness? What is the baseline against which we will judge any measured change?

One approach would be to fund IRB demonstration projects at selected institutions to demonstrate the effectiveness of proposed rules prior to more general implementation.

Personally I am concerned that any shift away from the use of local IRBs will undermine the effectiveness of our current system for protecting research participants. There are many advocates for the development and use of centralized IRB review, mostly from industry and large cooperative research groups.

Admittedly, there are many administrative problems that arise in the coordination of multiple

IRB reviews and the unjustified degree of variability among IRBs in the efficiency and quality of their review.

Although I am certainly a layperson when it comes to law enforcement, let me suggest an analogy between the local IRB and community policing. The local IRB walks the beat and knows the neighborhood in a way that is not available to a central IRB. The local IRB can balance regulatory compliance with a flexible interpretation of the law, forging a partnership with investigators that ultimately serves to protect research participants. Support for the local IRB may be expensive and administrative complex, but crime will go down.

To take the IRB off the beat and put them in the station house is not the solution. To remove any regulatory authority from the local IRB and place it in the hands of a remote central administration is not the solution.

I suspect that the effectiveness of advice from a community based police officer is partly related to the baton and handgun resting at her side.

At the risk of pressing the analogy too far, or perhaps of having even started it in the first place, the decisions and actions of the local IRB must be supported by the institutional

administration, yet with feedback from the community that the IRB is designed to serve; that is, the people who are research participants.

We have many issues that call for our attention. The definition of research, investigator conflicts of interest, recruitment incentives that may unduly influence the consent process, ongoing data monitoring and preventable research risk, the development of meaningful outcome measurements for IRB review and the ethical conduct of research, appropriate empowerment of an IRB to make necessary yet unpopular decisions, building a meaningful culture of protection rather than focusing on simple regulatory compliance, and many other important and vexing issues that haves been mentioned by my colleagues on this panel or that have come before you at other meetings.

The fact that we recognize and are engaging these issues is a sign of the health of the IRB system and not it's disease. What is needed now is leadership guided by moral wisdom and informed by a dispassionate analysis of the facts.

DR. SHAPIRO: Thank you very much and let me take this opportunity to thank once again all the participants on the panel. We appreciate your generosity in taking time to be here with us today.

Let me now turn to see what questions that

may arise from members of the commission. Any questions?

Larry?

DR. MIIKE: For Mr. Stinson and anybody else who wants to comment. On the issue about decentralized research projects and the multiple affiliations, what would you propose be the institutional response from the oversight agency, the federal government?

And, also, along those lines, right now there is really the office of -- the old Office of Protection from Research Risks, and then there are funding agencies. So is there an appropriate decentralization at the federal level, too, in terms of oversight?

And then for Ms. Keane -- well, let me -- I better stick to one question at a time.

DR. SHAPIRO: That is a good idea. Yes.

DR. STINSON: Thank you.

As it relates to the decentralized function I personally believe that we need to pay particular attention to what we mean by community because as we move into these extremely distributed decentralized systems, it will be very difficult for us to understand what is going on throughout particularly the State of Michigan.

In our's we are doing projects in the

Charleboyd (sic) area, which is probably four or five hours away. We are doing it up in the UP, which is a good 10 to 12 hours away. We are doing it in Wisconsin which is 15 to 17 hours away so I believe that there are going to have to be some type of shared responsibilities from IRBs from the local level when they do exist and they only exist particularly at health care institutions.

They do not exist within maintenance organizations or individual physicians and we will have to address that.

I do believe that that has to be at the institutional level and I find that very difficult to think that we can implement a system where we have to get sign off by some type of government agency for that. I think that has to be included into a major educational program that would include those individuals knowing about what it means to be part of research at Wayne State University.

One of the concerns that I do have about the educational programs is we believe that an educational program is for IRB work. My personal opinion, the education is -- how it is implemented at the local level. So what is acceptable and approvable at Wayne State may not be acceptable and approvable by NIH.

What they have in their training programs

and how they define and what they tell investigators to do will be exactly the opposite of what should be done at Wayne State.

So I think we will have to pay particular attention to that educational function.

DR. SHAPIRO: Thank you. Larry, do you want to ask another question?

DR. MIIKE: Yes. Do you have a formal or loose network or association of institutional review boards because I was struck by your comment that the feds are the only ones that you can turn to when you have an issue? And it seems like -- you know, with the internet and listservs and et cetera, you could have best practices kinds of things. That has been raised before.

MS. KEANE: I will start answering that but I think I will defer to Skip Nelson. Yes, there is a network of IRB administrators and we do find tremendous value in interacting professionally.

The Association for Research -- Applied Research Ethics National Association, ARENA, which is a branch of the PRIMR organization, is of tremendous help and resource to IRBs who feel isolated. IRB staff members and committee members feel as if they are often operating in a vacuum so that is of tremendous support.

Skip, do you want to talk about the McWIRB?

MR. NELSON: Since 1994 I have been the coordinator of an IRB discussion forum on the internet which is currently web based. The URL is www.mcwirb.org, which stands -- used to stand for the Medical College of Wisconsin IRB, where I no longer am located so now it is just a nickname. And there is now 2,300 people that are members of that.

And it is expressly for sharing that information.

I will say, though, I think sometimes people are reluctant to get very sort of down and dirty about specific protocols in that kind of a forum because e-mail in many ways is not private and can be circulated and there is a capability of having private discussions in password protected locations but by and large e-mail is what most people use.

DR. SHAPIRO: Mr. Stinson, do you have a comment on this question?

DR. STINSON: Yes, I do. It is my personal opinion that it would be extremely helpful if federal agencies that are working with institutions in terms of education, in terms of compliance, would be separate from any compliance type issues.

We do that in areas of scientific misconduct where we separate the office that makes the decision about what the consequences about being

out of compliance from the person that makes the judgment that, in fact, you are out of compliance.

And I think if we separated that, that it would make it very helpful and easier for academic institutions to approach a federal agency to talk about an issue when they know that that group is not going to be the one that is going to be providing punishment.

DR. SHAPIRO: Thank you.

Bernie?

DR. LO: A number of you commented on the importance of having a local IRB presence even in this new world of multicenter community based research. Certainly we have heard that sentiment from a lot of other people. Could I ask you to give some specific examples of the sorts of situations where a local IRB would have insights that would make a difference in the protection of human subjects? I would be interested in both an example where the local IRB said, "Yes, it is okay to do it here even though it could never be done at Bethesda," or vice versa, "Even though Harvard allowed that to go forward, we are not going to allow it because of -- not just because of variation but because there is something about the institution or the investigator."

Does it work on that level or is it just

that we are kind of different?

MR. NELSON: Yes. I think it works on that level. I think any of us have investigators -- again it is just the nature of the beast. Some who you can leave on a longer leash and some whom you keep on a shorter leash. It does not mean they should not be doing research necessarily but they may not have attention to detail in the same way that others, for example, might have.

A truly centralized mono-IRB set up such as might exist in industry sponsored studies run at private practices around the country and then run out of -- are overseen by a central IRB, the extent of their interaction is typically, as I said, getting the state medical license and a copy of their CV, and they say, "Okay. You know how to do research." And that may or may not -- we have a pretty good feel at least at a local level on, as I said, the capabilities of our investigators.

We also have examples of stands that we have taken on nationally run studies that -- not because of any local restrictions but just there is an advantage -- you know, two heads being better than one. We have seen situations where studies -- the Women's Health Initiative is an example. It was approved nationally. A huge -- sorry -- a huge study involving tens of thousands of women.

They had already deposited several million and some dollars in the UNC bank account when our IRB got a hold of it and this was before the days of just in time review, and it took somebody on our IRB to say giving unopposed estrogen to women with their uteri still intact is not current standard and they would not allow it to go on at our institution.

That fortunately was a scenario where that information could be passed along back to the central level to NIH in this case, and the whole Women's Health Initiative was redesigned because of one member on one board happened to raise a question.

So there is some strength in numbers, I guess, is another thing that factors into that.

DR. SHAPIRO: Mr. Stinson?

DR. STINSON: I might give an example. At Wayne State we include IRB review for eight other health care facilities. Three of those are in the suburbs, the other five are in the metropolitan area.

The difference in the demographics of that is within Metropolitan Detroit. The community is 80 percent African American whereas in the suburbs it is exactly the opposite. 80 percent is Caucasians and other -- particularly Orientals.

And so there is certain research projects

that we will approve in one particular area or in a couple of cases we have made modifications to the consent form when it is going into a sensitive group. And so that is an example where even within our IRBs we make decisions that would affect how we go with research.

DR. SHAPIRO: Thank you.

Yes, briefly.

MS. KEANE: Very briefly. I want to emphasize that in the behavioral research areas community tolerance for risks and for access to certain populations is best understood by the local IRB and that is an area where I think that the local flavor is very important.

DR. SHAPIRO: Thank you. I have quite a few commissioners on my list now so try to keep our questions focused.

Jim?

PROFESSOR CHILDRESS: This is directed towards Skip Nelson but I would welcome any comments from others.

A number of people have proposed Data Safety Monitoring Boards as at least a kind of supplement, valuable supplement to the system we currently have.

Skip, in your remarks on page 4, in a very compact sentence, you raise questions about this

shift not being well thought out and may undermine the protection of research participants. I would like to get you to say a bit more about that. I am not quite sure how it undermines research -- protection of research participants, in part, because the contrast you draw between Data and Safety Monitoring Boards, folks mainly on data reaching a predetermined level of statistical significance, in contrast to information pertinent to the willingness of current participants to continue in research.

I am not sure how -- and please inform me -- I am not sure how much information is actually provided to current research participants as a trial goes on that would be really pertinent to their decisions to continue anyhow so I am not sure that having a Data and Safety Monitoring Board function would actually in any way undermine that.

And it seems to me that given the inadequate monitoring that we frequently hear about of IRBs in relation to ongoing trials there might be at least some value there. So what I would like to get you to do is say a bit more about this one sentence.

DR. NELSON: Part of my concern is the extent to which we have not fully worked out what a Data Safety Monitoring Board would do in any kind of

public way. And the variability i models could range simply from a decision that it crosses a statistical point to a very careful consideration of whether or not adverse events are occurring at a frequency, even if not reaching statistical significance, need to impact on whether the study continues or whether people need to be informed.

My concern is we have not worked that out or talked about it, or established standards for that.

When I, as IRB chair, as I have started over the last couple of years, have asked for the reports of Data Safety Monitoring Boards, I usually end up getting a letter that says something like the Data Safety Monitoring Board has met and decided that the study ought to continue, period. And I think that is clearly insufficient.

So, I just think we need to think it through rather than simply appeal to that board and then as a black box it will solve our problems. I agree with your comments. I think this is influenced somewhat by an article that came out in IRB in January/February that talks about the tension between statistical significance versus whether someone would be willing to remain in a trial even with that information.

DR. SHAPIRO: Any other? Mr. Nelson,

briefly.

MR. NELSON: Just very briefly. We recently had a think tank on DSMB-IRB interactions that was held at Duke University and representatives from all those communities and Ernie was there, and others, and I went into that conference really aching for DSMB reports to be relayed on because, as Skip has alluded, there are mandates coming out of NIH dated June of '98 and June of '99 that first established DSMBs for multicenter studies and then in June of '99 demanded that those aggregate reports be passed along to IRBs.

I can tell you, and I told NIH at that conference, and they were surprised to hear it, that those reports are not being passed along. We engage in a huge number of cooperative trials and rarely see a DSMB report and when we do it may be a letter just that succinct.

The other thing, by the end of this two think tank I was really disheartened because having gone in thinking they can perform the role that we are poorly equipped to do, by the end of the conference when the DSMB people told us how they actually operate, it was disheartening to learn that they actually consider some of their information proprietary or they make decisions not to pass things along to an IRB. So the very group we were

going to pass the buck along to in some way was not feeling free to communicate with us.

DR. SHAPIRO: Eric?

DR. CASSELL: A number of you talked about how important it is to educate your investigators and your IRB. Would you be more specific about who would do the educating, how much education you are talking about, and when it would take place, and who would pay for it?

MR. NELSON: Those are all questions we are asking with the new NIH mandate that says go out and educate but stops at that point. We know we can get shut down if we are not doing it well enough but we do not know the answer to many of those questions.

DR. CASSELL: Well, then what would you like?

DR. STINSON: I can make a statement on that. Really in my original presentations I had a section on that and decided to remove all issues of costs because of time factor. Certainly the education program has to be varied and it has to be consistent over a long period of time. It is not a one time I have taken the course, give me a certificate, let me send that in to NIH.

Activities change. There has to be modules related to various types of research so it is my own personal opinion that there will be a basic module

that our investigators will take and then for those dealing with selective audiences like prisoners, pediatric patients, there will be additional modules.

In terms of costs, there is a great deal of discussion as it relates to whether we ought to charge in the direct costs for the IRB review. It is my opinion that that is detrimental to our overall efforts because our program is more than just IRB review and approval. It is the program that determines whether you have successful interaction between the physician and the patient as it relates to informed consent about participating in the research.

If you are only going to pay for the IRB review, that is probably all you are going to get. Everything else is going to be minimized. My personal opinion is it would be far better if we would include it in that indirect cost and remove the indirect cost. There is a pool for all of the compliance issues and that needs to be moved out and out from underneath it.

There is currently a cap of 3.5 percent for administrative costs on the indirect cost pool. So all regulation and all types of education programs, if they are funded by the granting agencies need to come out of that.

My personal opinion is compliance issues need to be pulled out of that and we simply pass those costs on to the granting agencies for that portion for which they are supporting. So if we are having an education program, we ought to be able to recover that in our indirect costs, not simply have that included in a cap with everything else that is included within that cap and that includes the participation of individual physician and health care professionals as members of the IRB.

3.5 percent is way too low for the administrative burden that academic institutions are asked to adhere to.

DR. NELSON: One quick comment -- the IRB chair, in addition to the administrative support. That is one reason why I think local IRBs are important because if you remove that you remove a chair. And I find most of the effective education I can accomplish is in the course of discussing design of protocols and the actual conduct of the research informally one on one in a case based approach as opposed to a classroom approach.

In terms of funding it, I think we need to get to the point where that chair position is seen at a medical school, for example, in the same way being dean of students is. You do not find anybody in the dean's office not having support for time

spent in that activity.

DR. SHAPIRO: Thank you. Diane?

DR. SCOTT-JONES: My question is a follow-up to a comment that Dr. Stinson made earlier. You mentioned that it might be useful or that you have on occasion changed a consent form to accommodate various population groups and I was wondering if you could say a little bit more about that. I can imagine that one obvious change would be language. Say if you are in a Spanish speaking community you might need to translate the consent form into Spanish.

But what are some other kinds of changes that you might see as appropriate that we should think about?

DR. STINSON: There are certainly areas in groups of people who will not respond to a requirement for written informed consent. When I was at the University of Texas Medical Branch in Galveston we had an extremely large Vietnamese population who when you put an informed consent in front of them automatically rejected it. They did not ask any questions. They did not want to know but because of the heritage that they had in terms of the government in having a document that a person signed, they would not discuss anything as it relates to research if the IRB required written

informed consent. We certainly had issues of language.

We have a project at Wayne State that is the interaction between the Arab community and the African American community, and the dialogues that have to go on between those two groups, particularly within stores, convenience stores, where one group happens to generally own most of those and the other group is the people who will patronize those. And so we had to make some refinements to a consent form to reflect that.

Those were some areas where we have had to make some changes.

DR. SHAPIRO: Thank you.

DR. STINSON: Did you understand that? I saw your eyebrow sort of wink there.

DR. SHAPIRO: Are you satisfied, Diane?

DR. SCOTT-JONES: Yes. I was not quite sure what you meant about changing consent for the Arabs and African Americans in Detroit.

DR. STINSON: Well, in that particular one it was about the documentation and the fact that we were videotaping those interactions. Really what was happening, we were taking the security cameras, the film from the security cameras and using that as research data. And so one group was much more sensitive about that then the other one.

DR. SHAPIRO: Alex?

PROFESSOR CAPRON: A comment and a question for the panel. The comment is that we have heard from several witnesses now concerns about IRB access to and sharing of proprietary information. We have heard about the relationships to the Data Safety Monitoring Boards. We have heard about what information coming out of the partial statistical analysis would be conveyed to subjects and I want to ask quite explicitly that staff begin to develop some responses on these issues.

I think that the latter issue is a particularly complex one because on the one hand there is a sense that subjects in research should have all the information, all the relevant information. At the beginning of a research project we allow the researcher and the IRB to apply some kind of scientific standard as to what information is relevant, the fact that a drug has had certain adverse consequences in anecdotal use would not necessarily rise to the level of saying that there is a danger that you ought not to do this, and part way through a trial the data from a scientific point of view may be equally unprobative, and I think we need to think about that, and I hope that the staff will come up with it.

My question for the panel is about the

risk/benefit and the risk assessments, and certainly a good deal of what you all have said, and I have heard you all be quite uniform on this issue of the local variation and the value of local IRBs based upon local knowledge, and nevertheless I think from a public point of view for a long time there has been a sense that it is somewhat bothersome if IRBs look at the same trial and some approve it and some do not.

And part of the explanation can be we know our local community, we know their sensitivities, we know there are investigators here who can handle that, at another IRB they do not think the investigators can handle it.

But what I wanted to get a sense of is do you think there is any uniformity on the assessment of risks? Is there any resource to which IRBs can look? Sort of an encyclopedia of agreed upon risks for certain procedures?

I mean, whether it is a blood draw or a CAT scan or a psychological testing instrument. Because if variation is occurring because IRBs have wildly different ideas about what at a statistical level the different outcomes are from the use of different interventions with particular populations, that is a more bothersome and maybe even indefensible reason why certain populations would be exposed to research

and others would not or conversely certain populations would have access to whatever benefit comes from research and others would not.

Has the IRB community ever developed anything like that?

MR. NELSON: We are all looking at each other wondering who is going to tackle that. In response to your first comment, if your staff is going to dive into that, I will just refer them to Jeremy Sugarman and Rob Kaliff who brought together this think tank at Duke on the DSMB-IRB interactions and are putting together proceedings from that conference.

But the -- along with the issues that I and everybody else raised that you have just alluded to, also on my list of issues and problems was the variability that you have also just alluded to, and it is a problem. I think the question is how to have our cake and eat it, too, to maintain and preserve that local knowledge of customs, of norms, of patient groups, of investigator groups but yet have some more of a consensus approach to the big ticket items.

I do not know that there is a dictionary or an encyclopedia. I think a positive step was the relatively recent -- I think it was November of '98 when the expedited review categories list was

expanded with examples of different categories and that at least take a baby step with agreement, surprise, surprise, between FDA and DHHS, which was also positive, toward identifying and giving us some better guidance than we had rather than just saying nebulously defined minimal risk, go at it, they started to put some context there and some examples. That has been a positive framework from which to make some of these decisions.

DR. SHAPIRO: Mr. Stinson?

MR. STINSON: I would simply like to make the comment that an IRB is made up of individual people. Many of those are physicians whose standards of care differ from their colleagues. So you find what is the standard of care within the Detroit medical center or particularly Detroit Receiving is substantially different than what is acceptable at the Medical College of Georgia where we happen to have a joint project going.

Because those standards of care vary, also the perceived risks associated with that vary, and so you have got professional judgment coming into play there. So it may be very difficult, and I think that is the reason why there has been some reluctance about translating that down to some numbers or something.

DR. SHAPIRO: Dr. Nelson?

DR. NELSON: To make a distinction, I think what I hear you asking is all of us could agree about hopefully the risks of a blood draw. In different hands bruising may be more of a risk than in other hands and that is where the local variation might come in. And in the assessment portion would be whether we would or would not consider that minimal risk and there will be variability.

I would hope there is no variability in simply the list of what could possibly happen. There would be local variation in the percentages of that risk which may reflect some of the differences that were just referred to and then wider variability and whether that does or does not constitute minimal risk in the assessment of how that would be incorporated within the protocol.

I agree there should not be much variation in just what we might state are the facts but you very rapidly develop variation.

DR. SHAPIRO: Thank you. I want to ask the commissioners who want to still speak to direct one question at one person and despite the great resources we have at the end of the table let's not ask all of them. We just cannot get through this list and we have a schedule to keep to.

Steve, you are next.

MR. HOLTZMAN: Thank you all for your

testimony. I will direct it to D. Nelson because I think he has a broad role in PRIMR and ARENA relative to us.

We sent out a letter to over 4,000 IRB chairs in connection with this project to ask them their thoughts. We have gotten back 11 so far. But nine percent of them, namely one of them, made the following statement.

(Laughter.)

DR. SHAPIRO: We may need a DSMB to figure that out.

MR. HOLTZMAN: I will quote from it. "The progressive commercialization of medical research by market forces and the corrosive role that pharmaceutical companies play in this process represent a major threat to the autonomy of the IRBs."

My question is, is that consistent with your experience, number one? And, number two, if it is, thoughts and suggestions to the pharmaceutical industry so we would be somewhat less corrosive.

MR. NELSON: Whether corrosive or abrasive or demanding, I am not sure which adjective to use. But on your first point I think it is great that you sent out letters. We got our's. I do not know if we have responded but I guess we are responding by coming here today. But I hope you get more because

that is very positive that you solicited that input.

I would say that we, and I suspect the vast majority certainly of institution based IRBs feel like we have a pretty free hand to take the right stance and to do our jobs. In other words, yes, there is pressure from industry.

It is relayed through our investigators who are told in no uncertain terms, look, you need to hit the ground running because we have an enrollment target and it is going to be hit by such and such a date, and it might be a few months away. So if your IRB takes two months to get an approval to you, you might as well forget about participating.

Well, that is a pressure that gets translated through the pipeline but I cannot say we have changed -- we, too, as Ernie said, view our relationship as a partnership. We like to think we are facilitating research and helping it go on in the right way.

We have moved to a weekly IRB meeting primarily to deal with six hour IRB meetings, which is a drain on anybody just to get through the volume that we have. But also a secondary aim is to be more responsive and to help people hit the ground running when we can.

I suspect that there are many good central IRBs and I have a great deal of respect for many in

that community. The independent or commercial IRB community. They are closer to being subject to that kind of influence because, in fact, they are a business, too, and their livelihood depends on being responsive to another business entity, the pharmaceutical sponsors. And that is not to say they bend over backwards or let themselves be twisted in knots either but they are more exposed to the -- they are vulnerable, if you will, using yesterday's talk.

We have very little direct interaction with sponsors and we kind of like it that way. We view -- we hold our investigators responsible and let them know that they are responsible at the local level and one way of doing that is to ensure that communications flow in between -- flow through the investigator from sponsor to IRB and back in the other direction, and it keeps them in the loop and lets -- sends a message that they are in the driver's seat.

When I have directly communicated with sponsors it usually is not a happy experience for either of us because they have different goals in mind than we do. I think there is a lot for cross talk there and cross education as to mutual needs and obligations and expectations. How to accomplish that, I am not sure, but there is some tension

there. We are viewed as the bad guys.

Increasingly, however, there are other parts of the bureaucratic system in place at certainly large institutions in addition to just the IRB. We are no longer the only whipping boy in town. There are offices of contracts and grants or offices of research services that, in fact, take longer to work through the system than the IRB often does these days.

DR. SHAPIRO: Thank you. Trish?

PROFESSOR BACKLAR: I would like to thank you all for coming. It is very edifying for us to have this discussion. I actually want to go back to something that Dr. Stinson said and I am not certain that you answered a problem that you brought up, which was a community of people who were afraid to sign the informed consent form.

I am wondering how you dealt with that?

DR. STINSON: Well, under the regulations the IRB can waive informed consent or the documentation of informed consent. So in that particular case what we did was that we did have an individual who participated in the informed consent process with the investigator and with the research subject. That individual had to be -- in this particular case it was Vietnamese and understand the Vietnamese language, and they documented that the

individual actually did give consent to participate in the project. So it was the observer that documented informed consent, not the research subject. The research subject would never have been willing to have participated.

PROFESSOR BACKLAR: Thank you.

DR. SHAPIRO: Thank you. Larry, you have the last question?

DR. MIIKE: No.

DR. SHAPIRO: Marjorie?

DR. SPEERS: This question is either for Dan or for Moira.

Very often when we talk about this issue of local IRB review versus a central IRB review we think of it in terms of the multisite clinical trials and so we think of it in terms of the -- of IRBs throughout the country, you know, and a trial being conducted in many different places.

The issue comes up also in the local setting where even within your own setting there could be five or seven or 42 IRBs that are looking at the same research study. And when we are talking about multiple IRBs in the same local area, in the same community, looking at the same study, then some of the arguments for local IRB, I think, seem to break down.

And so I would like to hear one of you

comment on this issue when what we are talking about are multiple IRB reviews occurring within the same community.

MS. KEANE: I will take a quick stab at that. I think we have two levels of concern here. One is local IRB review based on a community standard and understanding of the tolerance of participants for a certain project. The other is the standard of the IRB and not every IRB is as sophisticated or equal to the task. So even in a fairly small community area you could have varying degrees of capacity to review a project appropriately.

I do support some kind of neighborhood collaboration, if possible, to try to reduce the number of local IRB reviews that are necessary to satisfy a bureaucratic requirement. I think we have to look at that very carefully and decide how we are going to balance institutional risk and subject risk in that equation.

DR. SHAPIRO: Thank you. A comment?

MR. NELSON: Just very briefly. There are mechanisms under the current regulations and hopefully under the future regulation that provide some sharing of some cooperative review. The first time this came to our attention at UNC was when, Marjorie, yourself, brought it to our attention when

you were at the CDC and we entered a cooperative review agreement with a collaborative study that involved both institutions.

Certainly closer to home we have been increasingly using that mechanism. We do a lot of sharing of resources and investigations that take place at Duke at our institution. They are getting better all the time and we are interested in deferring to them when we can and vice versa, depending on the locus of the activity and the nature of the activity.

At some point deferring -- I do not know that that goes on a lot. I do not know that every institution is aware that that exists. And some institutions -- because it does get back to the protecting the institution part of what we do. I think certainly our primary role in life is to protect the subject but when we do that by default we start protecting investigators and institutions.

And university counsels like to keep things close to home for that sort of reason.

So there are some barriers to everybody sharing review even in the same neighborhood but there are mechanisms there.

DR. SHAPIRO: Thank you. Once again I want to thank all of you for taking the time to be here today. I very much enjoyed. Your comments were

very helpful to us. So thank you very much.

For the commission we will adjourn now and reassemble at 1:30. Thank you very much.

(Whereupon, at 12:27 p.m., a luncheon recess was taken.)

*** * * * ***

A F T E R N O O N S E S S I O N

PANEL VI: PERSPECTIVES OF THE OVERSIGHT SYSTEM FROM RESEARCHERS

DR. SHAPIRO: We are missing a few commissioners here but I would like to get started. Once again I want to thank all the panelists for coming here and sharing their thoughts with us. We very much appreciate the time you have taken to be here.

Before turning to the panel, Marjorie, is there anything you would like to say before introducing the panel?

DR. SPEERS: I would like welcome our panelists for this panel which will be looking at perspectives of the oversight system from the researcher's perspective.

This panel is comprised of four clinical researchers and just to remind the commissioners that you have heard from other researchers, particularly researchers from the social sciences and some of the issues that they have with the oversight system and the IRB system and today you will be hearing about issues and concerns specifically related to clinical research, biomedical research.

Let me introduce our panelists. The first is Dr. Susan Murphy, who is professor of pediatrics

at Northwestern University School of Medicine, and she is also chair of the Pediatric Oncology Group.

Second is Dr. William Burman, who is an attending physician at the Denver Department of Public Health.

Third is Dr. Monica Farley, who is professor of medicine at Emory University, School of Medicine, and on the staff at the Atlanta VA Medical Center.

And our fourth is Dr. Samuel Wells, who is director of clinical trials and evidence-based medicine for the American College of Surgeons.

Welcome.

We would ask each of you to make your opening remarks and after you have done that then we will open it for questions and discussion with the commissioners.

Dr. Murphy, would you like to begin?

SHARON B. MURPHY, M.D.,

PROFESSOR OF PEDIATRICS

NORTHWESTERN UNIVERSITY SCHOOL OF MEDICINE

DR. MURPHY: If I may, I just want to clarify. My name is Sharon Murphy.

DR. SPEERS: Oh, I am sorry.

DR. MURPHY: That is all right.

DR. SHAPIRO: Sharon.

DR. MURPHY: Yes.

I want to thank you very much for the opportunity to present the testimony to you today on a number of issues relating to ethical and policy matters regarding oversight of human subjects.

I want to share a number of concerns with you and provide a few suggestions but first, if I may, I want to give you some more personal background to provide you with a better idea of where I am coming from.

I am a clinical pediatric oncologist and I am testifying before you today from the point of view of a clinical cancer researcher. My research subjects, therefore, are not healthy volunteers. I lead also a busy hospital based subspecialty division of hematology and oncology at the largest children's hospital in Chicago where we currently have 61 open IRB approved protocols and we are enrolling approximately 50 to 60 percent of our eligible patients on clinical trials.

For the last eight years I have also been privileged to serve as chair of the pediatric oncology group, an NCI sponsored cooperative oncology clinical trials group, which annually enrolls over 1,800 children and adolescents with all forms of pediatric malignancies on two therapeutic trials, as well as hundreds more annually on biologic studies of translational research,

correlative science and cancer control and epidemiology.

The Pediatric Oncology Group, just to tell you a bit about it, we have over 100 member institutions and over 2,000 individual professionals in our group. And we have recently joined with three other groups, the Children's Cancer Group, National Wilms' Tumor Study Group and the Intergroup Rhabdomyosarcoma Study Group, roughly doubling our size and merging all of the pediatric clinical cancer trials groups into one. We have christened this baby COG, the Children's Oncology Group.

With the merger, our members are responsible for most of the cancer care delivered to children and adolescents throughout the entire United States, Canada, Australia, New Zealand and Switzerland, and we conduct nearly all of the pediatric cancer research in North America.

To supplement my presentation I have provided you with written background material detailing the extensive safeguards we have in place for protection of human subjects in our oncology clinical trials group. Policies and procedures which are, of course, in compliance with all the terms of our U10 cooperative agreement through which we are funded by NCI and in keeping with the Common

Rule and OPRR and NIH Guidelines.

So you can see I am speaking to you today with a great deal of familiarity and long experience both as a physician and as a clinical investigator involved both in single institution and multiple institution trials.

And though I am a pediatrician and deal with a particularly vulnerable and special population of research subjects, i.e. children with cancer, I also have a lot of familiarity with all of the NCI sponsored cancer cooperative groups targeted primarily to adults from my experience as chair of the cooperative group chairs for NCI and as a founding member of the Coalition of National Cancer Cooperative Groups.

A lot of the issues I will touch on relating to centralized IRBs later in my remarks actually apply equally well to all other large multi-institutional federally sponsored research endeavors.

Now in my daily work, I function thus at the interface, both as a physician and as an investigator. Indeed, in pediatric oncology the boundary between research and practice is not a bright line because clinical trials are the standard of care in our discipline. And the majority of children with cancer in this country are enrolled on

clinical trials.

Arguably, the spectacular advances in cure rates and overall survival for children with cancer are the result of this commitment to clinical research which characterizes pediatric oncology and makes us the model.

There is quite a bit of evidence that patients benefit from participation on clinical trials simply by being included in a rigorous research protocol. And there is, furthermore, a substantial body of evidence that the survival of children and adolescents with cancer is better when they are treated on clinical trials compared to those who are not enrolled on protocols.

Cooperative group trials you have to understand undergo extensive research to assess each new protocol concept on a number of things. The importance of the question being asked, its relationship to current standards of care, and the risk/benefit ratio for the subjects who would qualify for entry as detailed by the eligibility criteria for the study before the protocol even gets to the local IRB or to the potential trial participant.

Our trials and those of most sponsored groups typically incorporate reference laboratories enabling enlightened patient specific biologic

treatment stratification and providing the study subjects with the benefit of the most sophisticated diagnostic and staging practices available.

All our group clinical trials are reviewed not just internally but also externally by the NCI and by, of course, all of our local member institutional IRBs.

Toxicity is closely monitored. Adverse events are reported centrally, interim results are scrutinized at intervals by our statisticians and independent data and safety monitoring committees. Protocol outcomes are very carefully analyzed and reported, and lead to the establishment of improved treatments and elimination of ineffective therapies.

So I kind of take offense at the ethical concept of therapeutic misconception, which seems to me at least to be an oxymoron. And I do not understand why the definition of research presupposes some type of harm attached.

In preparation for this testimony I have really tried to put myself in your shoes as commissioners and, like you, I am deeply concerned about high profile tragic outcomes and highly publicized evidence of individual and institutional failures to adequately protect human subjects and follow acceptable standards for the conduct of clinical trials.

This hurts all of us and destroys the public trust. Placing pressure on you to expand protections and enlarge the scope of regulations. Simultaneously we have all heard Secretary Shalala and the Clinton Administration have announced several new steps to strengthen federal oversight, policing clinical trials and clinical researchers and IRBs, even including proposals for civil monetary penalties for violations.

You must be careful not to issue recommendations which risk strangling the biomedical research enterprise which would have the net effect of preventing access of patients to potentially life saving treatment on trials.

A great deal has been written about the crisis in academic medicine in this country and the clinical investigator as an endangered species on the brink of extinction.

The climate for research is deteriorating and I am quite concerned about the chilling and negative impact of sanctions and stepped up enforcement on our ability to recruit and train and retain the best and the brightest clinical investigators, who after all will be responsible for the future progress in research.

So I urge you not to throw the baby out with the bath water and to bear in mind why it is

that patients participate on trials. Many suffer from conditions for which standard treatment does not work and they hope for the chance to try promising treatments otherwise unavailable to the public.

Just witness the intense interest of cancer patients in participating in trials of antiangiogenesis agents. In a recent Harris Poll surveying public attitudes towards cancer clinical trials the evidence was overwhelming that clinical trials participants reported positive experiences. 97 percent of trial participants reported that they were treated with dignity and respect and received excellent or good quality care believing as well that by participation they got more care and attention and they benefitted both themselves and others.

Now I want to conclude my remarks with a discussion of issues surrounding informed consent and IRBs highlighting the rationale for centralized IRBs for multi-institutional cooperative group trials notwithstanding the previous panel that advocated for local IRB control. And the issues that I want to touch on are actually outlined in much greater detail in the written material accompanying my testimony prepared by colleagues from the Coalition of National Cancer Cooperative

Groups.

I believe it has hurt everyone that there are inadequacies in local IRB oversight of clinical trials but I am not so sure there is sufficient appreciation that most local IRBs at the present time are simply not adequately staffed or supported to carry out all the tasks they need to nor do they always have sufficient local expertise to ensure adequate human subjects protection.

So it seems inconceivable to me how federal agencies expect to hold local IRBs more accountable for research results, regulation of compliance, conduct of education, seminars, annual audits of safety protocols, and assurance that informed consent is obtained properly even to the point of direct third party observation of the process.

What are you thinking?

Add to that the local institutional attempts to use IRBs for purposes other than the protection of human subjects, including enforcement of legal or fiscal policies of the local institution and risk indemnification.

Serving on an IRB or, God forbid, chairing one is a thankless task and it is time for investigators, institutions and IRBs everywhere to pursue innovative strategies to ease regulatory burdens without compromising human subject

protection. One solution may be centralization of IRBs for multi-institutional trials, which at least would have the effects of reducing the variance in local interpretation of regulations and also cutting costs of compliance.

I call your attention to the last appendix in the written material submitted to accompany my testimony, which gives you a very careful assessment of the institutional resources required to maintain regulatory compliance to participate in multi-center clinical trials.

In there you will find details of the estimate provided that it costs $2,580 per patient enrolled on an intergroup cancer trial conducted at multiple sites to maintain regulatory compliance alone, not including any of the costs of actually conducting the research itself.

So I ask you to carefully consider what benefits in terms of prevention of harms or wrongs would come from added costs of compliance with expansion of rules and regulations or whether investigators or institutions will simply quit and conclude they cannot afford it or cannot stand it any longer.

Lastly, as you prepare your important report on oversight of human research, I would like to voice my concern regarding your draft

recommendation to extend the definition of human subject research to include such things as surveillance, program evaluation, quality improvement, medical records review or medical monitoring, thus expanding the definition of a regulated activity and potentially expanding the work scope and responsibilities of IRBs even further while creating more bureaucracy.

This strikes me as a bad idea which will surely hamper health services research and hinder efforts to measure and improve the quality of medical care in this country. And it also seems to me that observation and surveillance of medical outcomes constitutes good ethical and medical practice, and provided patient privacy is protected, presents minimal or no risk to patients. So why subject such activity to more regulation? Where is the harm?

In summary, I would really like to thank you for your attention to the concerns of researchers like me and I would be pleased to answer any questions about my testimony after the other speakers.

DR. SHAPIRO: Thank you very much and I also want to thank you for the very extensive written material you provided. It is extremely helpful, both the appendices to your work and the

actual document itself, so I want to thank you and your colleagues who assisted you in putting that together. At least I, speaking for myself, found that very, very helpful and it has been distributed to all members of the commission.

Now the way we run the panel, I am just going to ask for clarifying questions now and allow your colleagues to speak, and then we will get to more general questions.

Larry, a clarifying question?

DR. MIIKE: Just a clarifying question on the issue about -- that you had mentioned relating to the therapeutic misconception and that the majority of the children enrolled in your trials get -- are better off than those that are not.

Am I assuming correctly that you are dealing with the most difficult -- in your consortia you are dealing with the most difficult cancer cases for which there often is no effective prevailing treatment and if you are not -- if you are talking about better level of care, are you talking about not so much the effects of the experimental drug but all of the care that goes around being enrolled in a trial?

DR. MURPHY: Let me try and clarify. Thank you for the question.

We conduct Phase I through IV trials, if

you will. Phase III are the majority, are, therefore, for your "walk in the door" previously untreated child with any form of leukemia or solid tumor or brain tumor so they are not the worst cases. In fact, through research now approximately 75 to 85 percent of all children with cancer in all stages and types are curable.

We also do Phase I/II research for patients who have failed front line therapy. Now the other part of your question had to do with how did we -- I am sorry -- distinguish the treatment from the research?

DR. MIIKE: No. I am curious about the statement that those that are in the clinical trials get better care than those without.

DR. MURPHY: Actually the evidence I referred to is a substantial body of published work in pediatrics at least that it is not that they get better care, they have better survival rates, better outcomes. We believe the care to be excellent in the context of clinical trials and what is the standard of care in our profession, in our discipline, and I think you can just point to a large amount of evidence that supports the fact that patients enrolled on studies in protocols have better outcomes than those who are, in fact, off study, off protocol in our discipline.

DR. MIIKE: I just want to ask a follow-up question then. Is that a reflection that it means that most of these clinical trials are successful or is that a reflection of something else?

DR. MURPHY: It is interesting to speculate what it is due to. I personally think it is a reflection of the most modern, cutting edge, state-of-the-art comparison usually of leading alternatives that are well ration -- you know, the rationale is very strong and it contrasts with saying nonparticipants who may be treated with something already, for instance, off the shelf or published from a decade previously.

We are using modern approaches and we use a great deal of discipline in the trial conduct, that is to say including as, in your material, audits, compliance, performance review, toxicity monitoring and I think the rigor itself is what contributes to the better outcome.

DR. SHAPIRO: Thank you. Is there any other clarifying question? Again I want to give the panelist time to present.

Diane?

DR. SCOTT-JONES: I just have a brief follow-up question. So if the outcomes are known to be better, why is it still research and not treatment?

DR. MURPHY: Well, I suppose the answer is until we cure 100 percent of our patients we still have to improve things and currently a lot of our research focuses on measuring, for instance, not just the quantity of survival but also the quality, attempts to reduce toxicity, a lot of modeling biologic stratification so that we can tailor the therapy more directly to the risks of the relapse hazard, for instance, based on enlightened biologic understanding of the causes of cancer and genetic factors.

So there is plenty of research left to do in oncology in pediatrics as well as in, you know, adults. I hope that is clear.

DR. SHAPIRO: Thank you. Dr. Burman?

WILLIAM BURMAN, M.D.,
ATTENDING PHYSICIAN,
DENVER DEPARTMENT OF PUBLIC HEALTH

DR. BURMAN: Thank you. I want to thank you for the invitation to speak to this commission. I am a clinical researcher primarily in HIV and tuberculosis treatment. Like most doctors, I cannot speak without slides so I have a few here.

(Slide.)

I have personally seen in my career the dramatic improvements in clinical care that come from well conducted clinical trials. I have also

seen clinical trials protect us from treatments that initially looked great but did not work and so finally I am very concerned as a clinical researcher about the state of local IRBs.

As a clinical researcher, the current system is laborious, slow and exasperating. Therefore, I am grateful for the chance to present my concerns.

I will also give a little bit of my background because my remarks and my conclusions come very directly from my background. I participate as a principal investigator in a number of industry-sponsored trials of new drugs for HIV infection and opportunistic illnesses and then I also participate in several multi-center clinical trials networks. One, the Community Programs for Clinical Research on AIDS, sponsored by the NIH, and another, the Tuberculosis Treatment Consortium sponsored by the CDC.

And then finally, and I will direct quite a few of my remarks to this, I am a clinical investigator at an institution whose IRB privileges were suspended.

(Slide.)

I wanted to point out initially how concerned we are in my field about protecting vulnerable patients, and to illustrate that I will

just give you the background of the baseline characteristics of patients enrolled in a recent large tuberculosis treatment trial.

As you can see, the minority were whites. Most were other ethnicities, reflecting the demographics of tuberculosis in the United States. Many were born outside the United States and Canada. Most had less than a high school education and many had recently been unemployed, homeless, in jail, and had significant rates of substance use and daily alcohol use.

(Slide.)

In the Tuberculosis Treatment Consortium we have a committee on human subjects protection, which I am a member of, and some of the activities of that committee have been developing standard consent form templates using simple language at or below the 8th grade reading level. Just a hint of the problems that can come when doing this is that I have had my own local IRB say you cannot use this language, it is not our standard, and we have to point out to them that their standard reads at the 11.5 reading level, for example.

We have also simplified the so-called short form, which is used per the regulations to consent patients who do not read, and in many cases speak English. Again I will say that the OPRR sample

consent form that is on the website reads at the 11th grade reading level.

We are undertaking an initial evaluation of the effect of local IRB review on consent forms. We heard some perceptions from IRB chairs. I am interested in the data. What really happens when consent forms that are approved centrally go to a local IRB? And then finally we are starting a pilot project to have local IRBs cede their oversight to a central IRB at the CDC.

(Slide.)

In October of 1999, the IRB privileges at the University of Colorado Health Sciences Center were suspended. That included there could be no consideration of new studies. There could be no enrollment in previously approved federally sponsored or federally regulated clinical trials. That was actually quickly expanded to all clinical trials, period. Actually, all clinical and epidemiologic trials.

There was to be no further follow-up of patients previously enrolled without the written exemption from the IRB and all of this lasted for four months, and actually longer because at the end of four months all 2,500 protocols had to be rereviewed, a process which has taken many months.

The reasons for the suspension as quoted in

the letter from the FDA included failure to conduct continuing review of ongoing research and failure to prepare and follow detailed written procedures for conducting review of research.

(Slide.)

Let me just tell you about our IRB, and I will say I am not a member of it, and I am not revealing anything that is not available on the FDA website.

They had approximately 2,500 open protocols at the time of the suspension and were considering approximately 1,000 new protocols per year. All of this was to be done in 23 meetings of about three hours each throughout the year, at which time they approved approximately 25 protocols per meeting, as well as conducting continuing review and examination of protocol amendments and review of adverse events.

And then prior to the suspension, interestingly enough, the expectation from the institution was that the volume of clinical research would double in the next five years.

I listened to the comments of the IRB chairs about carefully considering local populations and I am left with skepticism. When does that happen in a schedule like this?

The bottom line is our IRB was overwhelmed completely. Many other local IRBs, I suspect most,

are in similar situations.

(Slide.)

A review in the Journal of the American Medical Association in 1996 concluded that local IRBs are operating in a pressure cooker atmosphere and asked whether they would "explode or change." The response to the crisis in local IRB function has been clear from the regulatory side. We need increased enforcement, make the existing system work, force institutions to provide adequate resources to local IRBs, but I suggest another approach is to ask why. Why are local IRBs overwhelmed?

I think the answer is the ascendance of multicenter clinical trials. Although it is difficult to find definitive data, and I will say that the lack of data about research oversight is remarkable, and I think there is little doubt that multicenter clinical trials are the dominant form of research in humans.

One estimate is the number of multicenter clinical trials increased by 42 percent in just five years. Another indication is that the recently developed NIH clinical trials website, which lists federally sponsored multicenter clinical trials, currently has a roster of 4,000 ongoing multicenter clinical trials.

The present human subjects protection was not developed for multicenter clinical trials, much less this volume of multicenter clinical trials, and the problems faced by local IRBs as a result of this expansion, I will say laudable in my view, expansion of multicenter clinical trials are simply the large number of protocols to undergo initial review, and then I said thousands, I should say tens of thousands of safety reports of serious adverse events.

Let me illustrate my concerns about local IRB involvement in multicenter clinical trials with an example.

(Slide.)

A drug, adefovir. This was a promising nucleotide drug with activity against -- <u>in vitro</u> against HIV, several herpes viruses and hepatitis B, so very potentially promising in patients who are co-infected with all of those.

Furthermore, in initial trials it could be given with once daily dosing and was well tolerated in the short-term.

However, when subjected to long term randomized clinical trials, 17 to 32 percent of patients developed nephrotoxicity. Fortunately reversible in nearly all of them.

On the basis of this toxicity and its

modest antiretroviral activity, an FDA advisory committee recommended against approval and the company withdrew the drug from further development for HIV treatment.

So my summary of this is that the system worked. A promising drug was evaluated in well conducted randomized clinical trials. An unexpected toxicity was identified and handled appropriately but it is important to look at how this all occurred with the local IRBs.

(Slide.)

Nephrotoxicity was identified at the data centers and the Data Safety Monitoring Boards of the randomized trials. After it was identified, investigators, and I was one, and patients were promptly informed, and I think very well informed in a brief letter from the Division of AIDS.

And it is important to note that local IRB review of the tens of thousands of serious adverse event reports from this trial did not detect adefovir nephrotoxicity and, in fact, could not have. It was impossible because they did not have the access to the data elements which would make the evaluation of those adverse event forms meaningful, specifically the denominator data. How many people were taking the medicine. And, secondly, what the study assignment was from double blind clinical

trials.

And so as summarized by an NIH panel, the receipt of data that are neither aggregated nor interpreted does not provide useful information to the IRB to allow it to make an informed judgment on the appropriate action to be taken, if any.

(Slide.)

So, in conclusion from this example, local IRB review of the thousands of safety reports from multicenter clinical trials is an example of an unnecessary redundancy in the present system. Data centers and Data Safety Monitoring Boards appropriately protect patients safety in well structured multicenter clinical trials. So local IRB review of these does not contribute to patient safety but does contribute to IRB -- the paperwork crisis of local IRBs.

Are there other redundancies? Like the previous speaker, I wonder if initial IRB review of multicenter clinical trials provides something good. We have reviewed the experience in our consortium with eight recent protocols and found no changes in protocol because of local IRB review by the 25 sites in our consortium.

But, furthermore, this review takes time and I illustrate that with this slide here. These are two recent studies done in our consortium which

has the unique aspect of being sponsored by the CDC that there is both a local and a central IRB. As you can see, the mean time to approval by the local IRB approaches four months. In some cases, it was as long as eight months. While the central IRB was substantially faster with about a three to four week approval time.

So it is unclear that local IRB review has positive effects on protocol but it is clear that this review delays research.

Finally, let me consider consent forms which should be an indicator of whether the local IRB is assuring that clinical research is performed in a manner fitting to local populations.

(Slide.)

The answer from studies over the last 20 years is that most consent forms approved by local IRBs are written at a completely inappropriate level. And I illustrate this with some data from a study back in 1980, although I could give you references for studies into the mid '90s with the exact same conclusion, which is that most consent forms are written at approximately the reading level of the Journal of the American Medical Association rather than at a level which is appropriate to the patient population.

So the data suggests that the kind of

careful customizing of consent forms to the characteristics and attitudes of local populations must be uncommon because it is not evident in studies that adequately evaluate this.

So in my outsider's view, local IRBs are drowning in a sea of paperwork generated by multicenter clinical trials and a critical review of the role of local IRBs in the oversight of these trials suggest that most of this activity is redundant and does not contribute to patient safety.

Furthermore, it is clear that local IRB review of multicenter clinical trials does introduce substantial delays.

My suggestions for a system for the future will echo some of my predecessor's comments.

(Slide.)

First, I think we need streamlined initial ethical review of multicenter clinical trials using a centralized IRB or a combination of central and limited local IRB. And I will just note several pilot projects in NCI in the Tuberculosis Trials Consortium evaluating that possibility.

The British have recently published the initial results of a similar system which are certainly mixed but I think are a step in the right direction.

I think we need standardized consent forms.

I think that most of the differences at local levels are due to IRB idiosyncracies and not differences in local populations.

I think the advantages of standardized consent forms would be to assure that consent forms are written at an appropriate level, to facilitate translation of those consent forms into the native languages of target patient populations, something that is very important for us in tuberculosis research, and to facilitate changes in consent forms as new information becomes available. That is a formidable process in the current system in which that has to go back through all 25 to 50 local IRBs.

(Slide.)

I think there should be no local review of offsite individual safety reports for multicenter clinical trials. Local IRBs and investigators should be sent summaries with context, not thousands of anecdotes.

Finally, we need better coordination between the different parts of the system. There need to be formal lines of communication between Data Safety Monitoring Boards and a centralized IRB as well as better communications between site monitoring groups and the IRB.

What then in such a system would be the role of the local IRB? I think education of

investigators and study nurses and all those involved in clinical trials is important and an appropriate function for local IRBs. I think there should be on site observation of the methods used to recruit and enroll patients into clinical trials.

I say that because most of the published abuses have been abuses in the consent form process.

Finally, I think there needs to be at the local level a much more detailed review of intramural research because it does not have the protections built into multicenter clinical trials.

My conclusion is local IRBs are in crisis trapped between the demands for more clinical research and the requirements of federal regulations that were not designed for multicenter clinical trials.

The crisis of local IRBs will not be solved through more vigorous enforcement of outmoded regulations. We need a thorough overhaul of the present system, modifying or eliminating those parts that monopolize resources and do not contribute to patient safety.

Thank you.

DR. SHAPIRO: Thank you very much. Once again, are there any clarifying questions? Yes, Alex?

PROFESSOR CAPRON: In your description of

the adefovir study you quoted from an NIH research panel the statement, "The receipt of data that are neither aggregated nor interpreted does not provide useful information to the IRB to allow it to make an informed judgment on the appropriate action to be taken, if any." What is the context of that statement? Was that connected to a recommendation?

DR. BURMAN: The context was not in the adefovir trial. The context was an NIH special review panel for multicenter clinical trials and the specific comments were directed to -- regarded local IRB review of off-site serious adverse event reports and the recommendation was that that be changed. I can provide the committee that report. I suspect you have it.

DR. SHAPIRO: Jim?

PROFESSOR CHILDRESS: Just a question of clarification. When you indicated that the Data Safety Monitoring Board notified investigators and patients, were they informed simply that the trial was being recommended to be terminated or what was the information provided?

DR. BURMAN: They were provided a letter which gave details of the toxicity, how it would be handled and the details for follow-up to evaluate the duration of the toxicity. So they were provided a lot of details about why the studies were stopped

and what actions would be taken.

PROFESSOR CHILDRESS: It is one thing to provide the information when a trial is being stopped but I guess I am interested in your reflections since this has been a theme throughout much of the day about what kind of information the Data Safety Monitoring Board could provide to IRBs and investigators along the way because there is a real worry about premature disclosure of trends leading to investigators being unwilling to continue the trial or to participate or to enroll patient subjects. I would be interested in your reflections.

DR. BURMAN: I agree with those concerns. I think in designing clinical trials we spend a great deal of effort in designing that portion of the trial and it is all laid out in advance these are the kind of differences that we might expect. This is how those will be evaluated at interim analyses. And I respect that process. I respect those statistics. I think if at an interim analysis those bounds are not breached, the trial should continue, and that interim information should not be released to investigators or patients.

I worry a great deal about the risk of prematurely stopping trials that then have a far different conclusion when they are carried to their

completion.

DR. SHAPIRO: Any other clarifying questions?

DR. MURPHY: Can I just follow-up on the DSMB because I am not sure it is appreciated that when they were set up and we in the cancer groups and other large groups instituted them, part of the guidelines is that they are supposed to have confidential conduct to their proceedings. They are not supposed to tell. So it is somewhat of a -- you know, ambivalence. They -- even as a group chair, I do not get any other different kind of letter than what was referred to saying the trial is going okay, keep it up, much less 1,000 IRBs getting interim detailed information.

PROFESSOR CHILDRESS: No, and I have served on DSMBs and certainly appreciate that, but again we have heard a theme that there needs to be more communication between DSMBs and IRBs and investigators and my point is only that we cannot have it both ways and that we need to appreciate the kinds of boundaries. I very much agree with the kind of comment that has been made.

DR. MURPHY: Maybe just trust rather than more communication.

DR. CASSELL: That is difficult in the absence of communication.

DR. SHAPIRO: That is trust is difficult. Thank you. Okay.

Let's go on. I really want to hear next from Dr. Farley.

Welcome.

MONICA M. FARLEY, M.D.,
PROFESSOR OF MEDICINE,
EMORY UNIVERSITY,
SCHOOL OF MEDICINE,
ATLANTA VA MEDICAL CENTER

DR. FARLEY: Thank you.

Let me also start by introducing myself and where I am coming from. This will be a little bit of a change of pace from what you have heard in the previous two presentations and I will keep my comments brief.

It is interesting, although there are some key differences in the kind of research an epidemiologist does, that some of our conclusions are exactly the same so I find that interesting.

But what I do is infectious disease research that is primarily epidemiology. There is -- I am university based. I also have a VA appointment. So I have that other element of a federal appointment. And the research that we do -- it is an emerging infections program and it interfaces as a large collaboration between CDC and

is funded by CDC as well as state health departments.

We perform research in metropolitan Atlanta. There are other sites around the country to have a total population base for the research of about 20 million. Our area specifically that I am involved in is about a 3.7 million, 20 county area of metropolitan Atlanta.

The nature of epidemiologic research, there are some important and fundamental differences between this and clinical trials in that this form of research may be more similar to the social sciences in some respects that I know you have heard about in prior presentations but it is primarily observational.

It may involve enhanced surveillance for diseases. In our case, infectious diseases. It may involve assessment of knowledge in attitudes and practices with respect to disease. It may involve assessment of exposures that might put one at increased risk for various diseases and again in my case infectious diseases.

So that in this case a patient is not subjected to any invasive procedure or given experimental drugs in a clinical trial setting.

Confidentiality issues and privacy issues are in my opinion the primary focus of protection of

patients involved in this kind of research and that is, of course, very important. The form of consent, I think, also -- it may take a different form in that in some case control studies assessing risk for diseases, we may be contacting patients and controls by phone, and in that case verbal consent is obtained and how best to deal with verbal consent and to fulfill the requirement for confidentiality and such, I think, are issues that are probably in need of further guidance.

In many cases it is the power. It is the size that is really what drives successful epidemiologic research and that a large population base is common. It may again involve multi-sites and collaborations between multiple groups, including people who may be in the public health sector, as well as private, university, federal. So it is -- the power of the numbers is really very essential to pulling out relative risks that may be important but small and needing a large population base.

So constraints that actually limit access to potential controls for such studies can, in fact, jeopardize the success of a study and pulling the important risk factor that is being pursued.

It also may overlap in the case of surveillance activities with legislative activities

of public health, and again, program evaluation has been mentioned earlier.

It may involve banking of specimens, either human specimens, serologic specimens probably is one of the most common specimens, blood, sera, that might be collected in an epidemiologic study that is collecting any kind of specimen. In our case bacterial or microbial isolates that have been isolated from a patient with a pneumococcal infection, a pneumonia, or food borne disease. These isolates actually have in recent times come into the forefront in terms of the interpretation of an isolate, is that a patient specimen? Is the bacterial isolate a patient specimen?

So the issues that we are dealing with are somewhat different. They may in some ways seem less significant and important when it comes to -- or in comparison to clinical trials and patients who are being observed for toxicities to drugs or treatments. But nevertheless it is a perspective, I think, that is important.

And I will just go through some of the problems and frustrations that we deal with, many of which overlap, and some might be somewhat unique.

The first that has been heard before is that the IRB requirements go beyond a single IRB approval and in our case, as an example, I am at a

university, I am at Emory University, I am also at the Atlanta VA hospital, the work is funded by CDC and being done at multiple sites around the country, and I am a collaborator with the Georgia Department of Human Resources, which is our state health department.

And in the case of a new case control study that would be coming into our emerging infections program, we would be sending it through four -- well, three formal IRBs and then a VA approval process that is separate but not a formal IRB. So it will go through CDC's IRB. It will go through the Emory University IRB. It will go through the Georgia State Health Department IRB.

This, as you can imagine, can be somewhat tedious. It also leads to opportunities for disagreement between IRBs and interpretation of: is it exempt, is it not exempt, is it research, is it program evaluation, does it require consent, does it not require consent? So there are many opportunities beyond just the simple minor modifications that occur as probably idiosyncracies of each IRB. So that we have found that our modification to the process has been that we require it to be a sequential process rather than trying to save time and submitting it at the same time to all three IRBs. We have learned that leads to multiple

amendments and submissions. Along the way if one IRB changes something, and we actually have to go through the paperwork of resubmitting the entire proposal to Emory's IRB based on a change at CDC.

So we do it sequentially and we start with CDC and then we go from there. And I think it is obvious that can be frustrating and it can certainly slow down the ability to get a project up and running. Timeliness in some cases is important in this kind of research and in many cases.

There is a new pneumococcal vaccine that is going to be used this winter season for children under the age of two. We want to start a case control study to assess pneumococcal vaccine efficacy of this new vaccine, recently FDA approved. This may be the only winter that we can adequately do this study because the numbers may fall off substantially with this initiation of the use of this vaccine.

So we have to struggle to get this through in a timely fashion in order to have it ready and it will be close at this point to try to get it through that many IRBs in the next three, four, five months.

The other issue is that with surveillance activities it very much leads to a confusion of that distinction between public health activities, public health surveillance.

Salmonella infections are reportable diseases in the State of Georgia. If we are doing salmonella surveillance as part of the emerging infections program, we are taking it from passive surveillance which is the normal system, to active surveillance. So we are enhancing the surveillance system for something that is legislated to be a reportable disease in the State of Georgia. Is that research? And it actually has been deemed research in the case of some of the surveillance projects. So that has led to some frustration of that line -- that difference.

Another example would be a survey of physicians to survey their practices when it comes to prevention of particular infections or a survey of a laboratory on methods they use to try to isolate a particular bacteria. Are they using the guidelines that are published? This has been deemed research if it is generalizable. If we are going to use the results of this to make a general statement about the incorporation of these practices in the United States.

So you can see that these are quite different although varying from clinical trials, yet fall under and are part of what the local IRBs are weighted down with in terms of reviewing these projects with the same rigor as they would gene

therapy intervention for a child.

The oversight system in our way of looking at things has been structured to primarily deal with clinical trial work so that we are often frustrated when those -- that system is applied and difficultly to epidemiologic research. When we are asked to do our annual reports we are given a sheet that says please list each patient that was enrolled and their social security number, some identifying factor, and it is really not relevant. We cannot do it that way.

When the General Accounting Office came to the VA to review our clinical research with respect to human subjects there were other similar misconceptions about our form of research that the -- how to deal with verbal consent became an issue. They wanted the charts pulled, and this is charts pulled from a population of 3.7 million scattered around 20 counties, to see the consent form in the chart, which is the standard of checking on some clinical trial work.

Well, that was not relevant and we had to go through a process of justifying ourselves in our approach to research. So it was -- we find that we are sort of a square peg trying to be fit into a round hole in some cases.

And the guidelines, because of that, seem

unclear in many cases. Interpretations may vary by institution and sometimes even within the institution or have changed over time. Surveys sometimes have been deemed exempt and more recently seem to be more likely to be deemed research and require consent.

Overall and the bottom line, I think, is that the process has become very time consuming. For 17 active projects for my work in particular, those 17 projects end up with 49 separate approvals and that is the initial approval, not to mention the amendments and the annual reapproval of the projects. So there is a lot of time and energy and cost that is involved in maintaining our oversight adequately of the patients in this case.

So my potential solutions or my suggestions are in many respects somewhat similar to those that have been described before with a few specific requests that epidemiologic research be looked at and some of the features of it be given some separate attention. First, streamlining and standardizing the process for our type of research, as well a centralized IRB oversight would, in fact, make great sense from our perspective or -- and, therefore, providing authority for a single duly constituted IRB approval to be acceptable to multiple institutions.

Establishing -- short of that, if we must have multiple IRB approvals, I think we need some guidelines for dealing with disagreement between IRB committees. Is there a hierarchy of approval? Does CDC's approval or interpretation supersede the local? We have had instances where a survey recently was deemed research by CDC whereas at the state health department, the investigators or the individuals who were going to be performing the survey had deemed it to be program evaluation. And so there was conflict and we will not get funding from CDC for the study unless we meet their IRB's requirements.

So how do we deal with that kind of disagreement? There really are very few guidelines for dealing with that.

So, in general, the development of clear guidelines and in that process we ask that the rigor of the oversight reflect the degree of risk to the patient.

I think we would like very much that the guidelines for noninterventional and primarily observational population studies and surveys to be addressed, whether -- in some cases be deemed nonresearch, but in the case of research be addressed in a way that is relevant to those sorts of studies and not trying to put it into the context

of an interventional study dealing with the concept of consent that may take other forms or even whether the consent is necessary for a subsequent chart review on a reportable disease, for instance.

We would, in general, caution against casting that net wider to take in things that would normally be interpreted as program evaluation that are essentially putting patients at no risk whatsoever.

And then, finally, the idea that this infrastructure has been built up. Many of us are being put into the position of having to fulfill many requirements and it requires a lot of staffing.

It requires a lot of administrative time and I think we do not have adequate materials and guidelines to refer to, to -- I have not been able to really learn in ten years of doing this kind of research -- I cannot predict what the next study will require. It is -- each one is kind of a new adventure so that I am never sure what the interpretation will be the next time we come through what seems very much like the previous study.

So guidelines, I think, would be helpful. And I think the funding is not always adequate to offset the cost of this enhanced protection of human subjects.

Thank you.

DR. SHAPIRO: Thank you very much.

Are there any clarifying questions for Dr. Farley?

Okay. Thank you very much.

Dr. Wells?

SAMUEL A. WELLS, JR., M.D.

DIRECTOR OF CLINICAL TRIALS AND EVIDENCE BASED MEDICINE, AMERICAN COLLEGE OF SURGEONS

DR. WELLS: Thank you very much, Dr. Shapiro, and I thank the commission for asking me to testify before this distinguished body. I should say perhaps also in a way of introduction and clarification that I am a surgeon and, like Sharon and the group chair of the Cooperative Clinical Trials Group, the American College of Surgeons Oncology Group -- this is the most recently funded of the cooperative groups by the National Cancer Institute. It is the only surgical clinical trial group funded by the federal government.

The question came up a moment ago about the importance of clinical trials in standardizing and improving care, and I might give you some examples of things that we have learned in the early days of this surgical clinical trial group.

The first: there are no acute toxicity criteria for surgical trials even though they exist for radiation therapy oncology groups, and radiation

therapy in the medical oncology groups, whether the adult or pediatric.

To be generous, I would say there is a faulty skills verification process. Many people assume that in clinical trials a surgical procedure, say a gastrectomy, is a gastrectomy is a gastrectomy. There is often marked variation in the failure to standardize these procedures which are critical components of many clinical trials.

Also, surgery has perhaps fallen under the radar screen of oversight and surveillance of some of the other trial groups. There is no FDA for surgery or a similar site component. A surgeon can perform a given surgical procedure that he or she declares is new. This often is not monitored carefully. The most recent example of this is laparoscopic cholecystectomy. There has never been a controlled trial comparing this procedure to the standard operation. Still in this country each year there are 4,000 common duct injuries with this new procedure, far more than one sees with the standard therapy.

Clinical trials in many ways, the way that we are setting these up, new skill verification and education components, will address many of these inadequacies.

Demands that medical science prove the

efficacy of accepted interventions and rapidly test nascent strategies for alleviating human suffering has increased the need for well-performed clinical trials. Clinical trials really serve as the front end of a spectrum that includes evidence-based medicine and outcome studies.

Ethical treatment of participants is a paramount concern in clinical trials in order to determine that safety that is not compromised and that beneficial treatments are made available as quickly as possible. Clinical trials must be monitored for both adverse events and clinical benefits.

Recently there have been calls to include a plan for monitoring clinical trials of all phases and complexities. Despite the layers and collateral methods of oversight, including IRBs, locally, the data and safety monitoring committees, the federal components, OHRP, the FDA, the NIH, and the private sector, there still are potential lapses in assessing patient safety.

I will attempt to compare the theoretical and actual performance of each of the entities responsible for trial monitoring and evaluate where lapses might occur and then perhaps offer some suggestions about how each might improve its performance and create a cohesive net to ensure

subject safety.

First, the clinical site. A fundamental step towards reducing the chance of compromising patient safety through fundamental error is for investigators and their staff to have a systematic approach to the conduct of human investigation and an equally systematic approach to the collection and reporting of data from human studies.

A basal level of training in the methods of clinical research should be good clinical practice, which has been defined as a standard for the design, conduct, performance, monitoring, auditing, recording, analyses and reporting of clinical trials.

Adherence to good clinical practice principles should ensure that the data and recorded results are credible and accurate and that the rights, integrity and confidentiality of trial subjects are protected.

In reality, very few investigators could be accused of deliberately putting patients at undue risk, although the lack of education and formal training of many investigators in clinical research and in the ethics of clinical research limits their ability to recognize potential lapses and the most desirable conduct of human investigation.

The regulations give a fairly nonspecific

description of the qualifications required of investigators. And I quote from the "Good Clinical Practice Guidelines of 1997," "Investigators should be qualified by education, training and experience to assume responsibility for the proper conduct of the clinical trial."

There is no minimum level of training required to meet these qualifications and many such investigators may not even realize that they lack truly important skills and they might not understand the implications and requirements for adverse event reporting.

We have multiple interpretations by different government agencies and by different regulatory groups in the medical products industry that sponsor clinical trials. These industry sponsors, eager to avoid liability, require extensive audits of the case record forms of studies versus the medical records of patients producing mountains of audit trails of questionable value to either the integrity of the trial or to its ability to reliably answer the question being asked by the trial.

Thus, investigators, instead of interpreting adverse events and putting them in the proper context, protect themselves and their institutions by following the letter of the law.

Instead of auditing and monitoring trials, they are merely reporting information in a form that cannot realistically be used efficiently to determine the risk/benefit ratio.

A lot has been said about institutional review boards. I realize it is the primary focus of this committee and I will say a few words about this. The Office of the Inspector General has identified several changes that may adversely affect the ability of IRBs to carry out their missio. These include expansion of managed care and reduction in the ability of clinical revenues to support research, increase commercialization of research, proliferation of multi-center clinical trials, research in new fields such as genetics and mental health, and above all, the rise of patient consumerism and its demand for access to clinical trials and to the research data. All the rigorously collected data are not available.

Many members of IRBs have reported that they spend much of their time on documentation, compliance issues and cosmetic changes to protocols. This activity may serve in order to protect the institution and patients.

IRBs often lack among the personnel, the expertise, to analyze the statistical issues on which many studies rely for determination of when

the rate of events represent a true finding and when it simply represents random variation. IRBs often lack the resources needed to handle administrative mandates. Adverse event reports have been identified as one of the major hurdles to an IRB's effectiveness.

Several hundred or more adverse events reports are reported to larger IRBs each month. Because adverse event reports are provided with little explanation of their significance and because IRBs do not have available aggregate data on adverse events, knowledge of the full safety profile, the drug or device or surgical procedure, or even knowledge of the number of patients enrolled, it is virtually impossible to make an assessment of the risk relative to potential benefits for a study participant.

Finally, IRBs are mandated to monitor clinical trials. They are given no guidance on how to monitor for ethical research practices, nor is there a method for regulatory entities to evaluate how effective IRBs are in assuring patient safety other than checking for paperwork compliance.

Data and Safety Monitoring committees are charged by the sponsor and the investigators of a study with protecting the safety of patients by examining the data for indications of harm to

subjects, either due to adverse effects of a test agent, surgical procedure, or marked benefit in a study arm.

In theory, a Data Safety Monitoring Committee should develop clear procedures and should be given a firm understanding of its role. In reality, some Data and Safety Monitoring Committees may be convened only after a study has started and the role may become dictated by the evolving needs of the study. There is still no consensus on the requirements for membership and member composition of Data and Safety Monitoring Committees. It is most disturbing that there are few individuals with this wealth of expertise required for membership on these committees, resulting in a potential shortage of Data and Safety Monitoring Committee members at a time when this need is increasing significantly.

Data Safety Monitoring Boards sometimes included independent study-sponsored investigators. In some cases, representatives of organizations that have funded the study may sit on the Data Safety Monitoring Committee. This represents, of course, clear conflict of interest.

Regulators: Although the FDA, the Department of Health and Human Services, OHRP, are the predominate regulatory bodies to ensure research safety, all federal agencies and groups that fund or

conduct research with human subject promulgate policies to which their protocols must adhere.

In theory, the regulatory body would provide clear instructions and the nomenclature would be agreed upon without producing contradictory guidance to investigators. The guidance would be developed with the working knowledge of the impact on the paperwork burden, cost and impact of doing studies that are necessary to advance human therapeutics.

In reality, the instructions are often confusing and contradictory. Furthermore, with respect to adverse event reports, regulatory requirements and definitions are unclear and also occasionally contradictory.

International harmonization is still incomplete. Compliance monitoring has occurred more frequently in response to obvious lapses of systems for ensuring patient safety rather than in a proactive fashion.

Finally, regulators focus more on compliance, especially with paperwork, than focusing on the impact of patient safety achieved.

As far as thoughts about how this might be changed, certainly formal training programs for investigators and clinical coordinators should be developed and implemented. Formal training should

be required as a prerequisite for all of those involved in clinical trials. The clinical site should submit plans for auditing and monitoring studies to the local IRB.

I would say they should even be included in part of the medical school curriculum. It is not part of post-graduate education for most residents, review committees or American Boards under the umbrella of the American Board of Medical Specialties.

IRB members should have formal training in order to recognize the important elements of ethical research. This will increase the likelihood that members focus on assessing critical components of a protocol. The Data Safety Monitoring Committees should monitor all multicenter trials. I feel they should report the results of their deliberations to the institutional review boards, which oversee the activities locally of the clinical trial research.

It is important that the FDA, the NIH, the federal government components, continue to clarify the requirements for monitoring patient safety on every study. The various regulatory agencies should convene a meeting of the representatives to rewrite a harmonious set of standards with an eye towards including mandates to take into account the new realities of clinical medicine and the changing role

of the capabilities of IRBs.

There should be more innovation in the evaluation of the efficacy of safety monitoring. Academic medical centers are in an absolutely key position to influence a national dialogue about monitoring subject safety on clinical trials.

The NIH should increase its commitment to the training of clinical researchers through the K-23 and K-24 mechanisms and provide funding for research on ethics and empirical experience with research methods.

It is important that support for careers in clinical research receive emphasis. The recently announced K01 grant mechanism to support training of new researchers in clinical ethics is certainly applauded and represents a best effort in this regard.

Clinical trials are absolutely key to increasing the standardization and excellence of medicine in all fields in this country and the oversight mechanisms currently in place have faults, are in many cases burdensome, and create onerous tasks for investigators and members of both the IRBs and the Data and Safety Monitoring Committees. Let's hope that this commission will give due diligence to this problem and make recommendations to correct these deficits.

Thank you.

DISCUSSION WITH COMMISSIONERS

DR. SHAPIRO: Thank you very much and once again let me express my gratitude to each of you. Let me begin our discussion with a question. Well, let me just state something and then ask a question. I mean, everyone who has appeared before us both today and on other days dealing with the issue of patient protection and oversight mechanisms and so on has talked about the necessity of increasing support for the IRBs. That is increasing their financial support, increasing the institutional support, in various ways increasing their education and so on. I think at least it seems widely accepted by those who have appeared before us that they just need to do that to just increase their capacity to fulfill their function, including possibly having more IRBs if they are going to be local ones because any single one may just be overwhelmed by approving, as I think you had some data, 23 protocols every three hours or something of that nature in your presentation.

But I want to focus my question on the issue which I think most of you brought up, that is there is going to be an increase -- the prediction is increasing number of clinical trials and multi-center trials. And, therefore, inferring from that,

I think, most of you or at least three of you said that the logic of that leads you to a centralized IRB because that would be an efficient way, it seems obvious it would be, in some sense it seems obvious that it would be efficient to do that with one IRB instead of 20 IRBs.

I understand that argument. It certainly would be efficient. But if I think about it in another way, namely what kind of ongoing discussion, mutual education and so on takes place in each clinical setting, it does not quite feel the same, the efficiency does not seem perhaps quite as attractive as it might because it removes the decision to some distant IRB and does not -- at least I can imagine that that would have some perhaps negative aspects.

Now in the case of these consortia which you are the head of one or at least participate in one, that seems to take place amongst researchers before you even get to the IRBs in some sense if I understood the material you presented.

Does that worry anybody at all, the fact that if we had a centralized IRB for these multi-center trials that that would sort of decrease the amount of attention and the amount of concern, the amount of conversation that goes on in each individual site regarding their ongoing

responsibilities to the participants in these trials?

Is that an issue? I am just inventing a nonissue? Or what is going on in that sense?

DR. MURPHY: I would not want to accuse you of inventing an issue but I think --

DR. SHAPIRO: It is pretty close, right?

DR. MURPHY: -- you have to look at, I think, the necessity to try some new approaches because as was pointed out by many previous speakers, I am sure, the guidelines that we are all working under have been promulgated decades ago, thinking one investigator, one institution, you know, one IRB. It is just a different ball game now and there is simply the reality that most IRBs are overwhelmed and I think that centralized IRBs would have several advantages, not merely just efficiency, which is not frankly what should be the driving force.

I think that they arguably might be able to protect human subjects better because they would be able to be constituted with individuals with required expertise as well as, you know, persons external to the research who could look at the ethical oversight and could give multi-site trials the kinds of reviews in depth that they frankly do not receive with hundreds and hundreds of local IRBs

that are just overwhelmed.

I think they could have a better composition and do a better job and one might even think of letting pilots go forward using centralized IRBs with almost differing missions, if you will, or differing oversight. For instance, IRBs overseeing mental health research that has been a subject that you have been talked about before.

You could have the right persons composing that IRB and they would do a better job of that kind of ethical oversight it seems to me. You could have cancer IRBs. You could have for some AIDS, epidemiology, you know. I mean, I use those examples. It does not make sense to me to think that every local IRB has all the necessary expertise to review all the research that is coming at it with thousands and thousands of trials in big academic centers. They are overwhelmed. That is just some thoughts.

DR. BURMAN: Speaking as someone who works with both the central IRB at the CDC and then with local IRBs, I can say that I think we get better review at the central IRB for precisely those reasons. It is not an IRB that is trying to review an incredible array of trials. They are reviewing a fairly focused array of trials and so we get a detailed, often very incisive commentary back from

them, which does result in protocol changes. Whereas, from local IRBs in the last six years we have never had an instance in which we changed a protocol because of a local IRB comment. So, I think I would take the opposing view, which is that I think a well constructed central IRB may well provide better research oversight than multiple overwhelmed local IRBs.

And I tried to hint at a couple other advantages of having a single standardized consent form. I will say as a researcher who tries to keep up-to-date translated consent forms in Vietnamese, Spanish, Korean, Ethiopian and other languages, it is virtually impossible to do that in which I have to send all those through two different IRBs, their translators disagree, and so what happens is that I cannot keep an up-to-date translated consent form. Whereas, if I had a single standardized consent form for all sites that could be translated once and then be used at all clinical trials, that is really communicating with patients, that is substance, and a lot of what I see is fluff.

ot DR. SHAPIRO: I think, you know, those are persuasive comments. However, I do want to point out that it seems to me that everyone who talks about centralized IRBs always refers to the local IRBs as both multiple and overwhelmed. Those things

are not necessarily the same thing. That is you could imagine IRBs that were not overwhelmed at the local level but they are -- many of them are. I understand that.

Yes?

DR. WELLS: I think how the local IRB or the institution would react to the decisions of the centralized IRB would have to be considered. It is interesting that the previous speaker who mentioned not having a consent changed or action by the central IRB. I think we would have some problems with that perhaps if you have say 1,000 sites or 500 sites. You might not have every institution agree with the activity or decision at the central IRB and the work could be absolutely onerous at the central IRB. The adverse event reporting, considering what happens in some single institutions, might be a full-time job. It is not necessarily bad and I can see some advantages to it but it would take a great deal of work and effort and integration to pull this off.

DR. SHAPIRO: Thank you. Let's see what other questions. Larry, then Alex.

DR. MIIKE: I am sorry but I am going to have to ask my question and get my answer and leave. This is for Dr. Farley.

You were concerned about expanding the

definition of research. We are, too, but the issue is how you deal in the operational sense. If one narrows the definition of research there is the danger that projects that legitimately need human oversight will fall outside, and then if you try to narrow the definition of research, I think we will run across difficulty in saying what is research.

The other way is to liberalize the definition of research but also liberalize the exemptions and expedited review process. And it seems that that -- the current way that it is done, there is confusion about what is exempt, what is allowable for an expedited review, but if one can make that a lot more certain so that one can take a look across this and it is a very simple process to do either the expedited review or the exemption, and then really focus on those areas that really need more scrutiny, it seems to me that would be the more rationale way to go.

DR. SHAPIRO: Dr. Farley?

DR. FARLEY: I think those are excellent comments and I agree fully. I think the idea of it passing through but having an exempt status where there is some measure of evaluation, but brief, and it fits into a defined category of exemption is good. We have dealt with inconsistencies in the application of exemptions and that is a frustration.

If we can get it very standardized and things will be easily portioned into the appropriate category, I think that would serve to free up the IRB panelists for the more detailed evaluations.

I do have to say as kind of a side comment to the previous discussion as well that I do think local IRBs will continue to need to look in some fashion at these protocols that have had centralized approval. And I do not believe there is -- that that is entirely negative, but I do think that the idea that they can do it in a much more cursory fashion with the confidence that there has been the rigorous and the expertise -- the expert panel has looked at it, that they then can look at if there are particular issues that are unique to their local area, but only quickly look at those issues and not have to go through at least the motions of doing the detailed expert evaluation where they may or may not have the capacity to do that and certainly the time issues are there.

So that if there were a way -- I am not saying taking the local IRB completely out of the process, but making it a more realistic approach, and the exemptions, having them fairly well categorized, would be one step of freeing up their time as well.

DR. SHAPIRO: Thank you.

Alex, and then Arturo.

PROFESSOR CAPRON: My major question is for Dr. Murphy. You were offended at the concept of therapeutic misconception and I thought I would like first to get you to tell me what that concept means to you.

DR. MURPHY: Well, as I understand it, it is the ethical concept that if the individual who is seeking to conduct the research is the same person, if it is therapeutic treatment oriented research, the same person who is the provider of the treatment, then there conceivably can be a misconception on the part of the subject that they are not necessarily giving consent for research but it is their treatment. It is an indistinct boundary between treating and research for the subject and also probably for the investigator.

I think I have the concept right.

PROFESSOR CAPRON: Yes. I think that we could refine the details a little bit but I wanted to make sure we were on the same page. Since we heard both from you and I thought even more strongly from Dr. Burman when he said that there are -- have been a lot of treatments that have gone through clinical trials and the -- what the trial did was to protect future patients from that treatment because they turned out not to be efficacious or safe

treatments, the notion that something that is in research is of unproven value seems to me to be a different statement about the potential harms that are involved than the fact that a lot of things which are used are used even though they are not perfect, either NQ or avoiding harm and side effects, or they are used because they have been used and they have never been well studied and they are simply part of general practice.

And I wonder if with that in mind, in the end is the fact that something is the only alternative for the pediatric oncology patients that the people in your group, your national centers around the country, are providing interventions for? Does that remove the notion that they really are still enrolled in research and it would be different for them if there were a proven therapy for their treatment, even one which had only recently emerged successfully from a clinical trial? Do you not see a difference between those two settings? What we think of as the research setting and the treatment setting?

DR. MURPHY: Well, first, I want to make clear that the clinical protocols to which the majority of the children in our group and in our institution are -- they are offered access to and the majority enrolled, they are not the only

alternative and not 100 percent of patients are enrolled on study.

They can receive the same -- well, perhaps not always the same treatment off-study, but a standard treatment and there are standard treatments.

And in the community many people use standard treatments for pediatric cancer so it is not the only alternative.

PROFESSOR CAPRON: I was trying to make the case stronger for what I understood to be your position. If it is not the only alternative, I think that only helps to underline the difference between being in a trial and getting an alternative treatment, doesn't it?

I mean, otherwise why do we distinguish the two?

DR. MURPHY: Well, I ask myself that a lot, too. I think the only distinction is that we carefully analyze the outcomes and that makes it research. The irony to me is some other physician can treat somebody off a study with an unproven nonstandard approach and not have to go through all this informed consent and regulation and they can, you know, have toxicity and deaths occur and it is never even reported. I mean, if you think about it, there should be consent for not being on a trial

sometimes, particularly when it is clear there is benefit to the enrollee.

I do not want to overstate that, but it is ironic when you think about the distinction between being on a trial and off a trial where in our setting sometimes the only research is that we just collect the data and monitor the outcomes.

PROFESSOR CAPRON: Yes.

DR. MURPHY: You know, it is -- and we may or may not have a new agent or it may just be a standard agent that is already FDA approved in a different drug schedule or dose or combination, and that makes it research.

PROFESSOR CAPRON: I guess what I am trying to get to is it does not seem to me that most people who are looking at this and use the term "therapeutic misconception" do so with any sense that being enrolled in a trial is necessarily more risky nor do they do so with any deprecation of either the value of trials or the intent of investigators, physician/investigators, and I think that if -- and the reason I am exploring this a little is that I suspect that your sense about it is not uncommon in the research community and if those of us who have used the term have created in your minds the sense that you are being attacked by that term, either we have to do more to explain it or we

should look for something else because I firmly believe that there -- that it is important for people who are participants in research trials to realize that they are participants in trials. Not because something bad is going to happen to them but just because it is a somewhat different setting than getting, as you put it, the same intervention off-trial. I mean, as a compassionate use or whatever where they are not going to be in the data.

And I may, as a member of society and potentially a beneficiary of the results of the trial, be very glad that the trial is going on and think that medicine would generally be better if there were more careful examinations of all interventions. So it is not at all critical of you. It is simply saying that it is a different animal in some respects and people should simply be aware and so it is not a pejorative term in that sense.

So I found this very instructive to understand why it seems that way to you and I appreciate your elaborating.

DR. MURPHY: I think you do need to work on the language then because it is -- I am offended by it sometimes and in our own institution even or in others there is the implication that, for instance, Phase I and II or early phase clinical research, has no therapeutic intent and nothing could be further

from the truth. We always approach a patient with therapeutic intent, usually with a solid rationale for why this is, you know, justifiable and where the risks will be justified in terms of the potential benefit.

So I do not like the idea to think that it is a misconception that there is a therapeutic intent. So thank you for that. I appreciate it.

DR. SHAPIRO: Okay. I have Arturo, then Eric, and then Steve and Eric.

DR. BRITO: I, too, had somewhat related questions for Dr. Murphy, and I want to thank all the panelists before I get to the specific questions.

Dr. Murphy, a couple of things struck me about your presentation and I apologize if in your writing there is more detail and I have not had an opportunity to read that, but do you see that pediatric oncology -- that that subspecialty is perhaps one of the reasons, as you state in here, that the clinical trials are the standard of care in pediatric oncology? Do you -- I have my speculations of why that may be so. But I would like to hear from you why you think that might be in that particular thing. For instance, is it because there is more animal models that you could test before? Is it because of things like that and why

that might be so?

And on the related question to something that Alex was asking, how common is it in pediatric oncology for the clinical investigator to be the same person that recruits -- that is the physician that, therefore, recruits and also is the investigator for that same patient? Do you think that in this field it is more common than in other fields?

DR. MURPHY: Well, I like to think the answer as to why the clinical trials are the standard of care is that it is -- I should not -- pediatric oncologists are better doctors.

(Laughter.)

DR. MURPHY: We do have, I think, more of a tradition of clinical trials and cooperative groups in our subspecialty. It has been established over decades so there is a culture which has then, therefore, been passed on in training and because it is primarily an academic discipline it is not practiced out in the community that much. I think it tends to be -- you can get your arms around the problem a little better.

I do not really know. It is not the animal model thing. It is just the way we are trained to think. That is the way we train our trainees to think. There is a strong advocacy patient-parent

commitment understanding that trials are good standards for care and that it is important to practice evidence-based medicine, which is what trials are all about.

I do not know. I think we -- it is all I can comment. It is curious and others have often asked that question but it is probably a lot of things.

DR. BRITO: Okay. And the second part to that question or the second question really was how do you feel then pediatric oncology because of that system that the clinical investigator is often the same -- the physician and also the recruiter and eventually the investigator?

DR. MURPHY: It happens. It is not 100 percent of the time but it is quite frequently. With more multisite large trials, though, there is fewer opportunities for everyone to be the study coordinator so most people are in the role of participant rather than the principal investigator.

DR. SHAPIRO: Steve?

MR. HOLTZMAN: Well, my comment, it is more a comment than a question is directed to the interchange between Alex and Dr. Murphy, and Alex is not here but what the heck.

DR. SHAPIRO: We can manage.

MR. HOLTZMAN: I am less likely to get a

response if Alex is not here.

(Laughter.)

MR. HOLTZMAN: That is an inside joke.

(Laughter.)

MR. HOLTZMAN: It has troubled me -- it has troubled me sitting here for a long time about the therapeutic misconception because as it were, we act as if there is only two kinds of animal. Over here you have got therapy and over here you have got research and this moral obligation to say to someone in research you may not benefit, do not be misconceived that you may not benefit. But, of course, as usual the world lies on a spectrum as opposed to two cases with a range in between. And so if you are dealing with a clinical trial where there is a placebo control and there is randomization, clearly you have to say to someone you may not benefit. That is research that looks like that second kind of animal.

But if you are dealing in a world of oncology and clinical oncology and pediatric oncology where off-label use is standard of care, and where research means I am going to look at off-label use systematically now to learn something from it, you are not talking about placebo controls and that is why there is a reaction that says this is not a therapeutic misconception. This is instead

rigorously studied therapy.

And I think maybe we need to in our report sort of lay out that there is this spectrum.

PROFESSOR CHARO: Hands up.

DR. SHAPIRO: Alta, yes. We have someone by phone. This is Alta Charo from the University of Wisconsin who has been on the phone.

MR. HOLTZMAN: Does that get at the issue?

DR. SHAPIRO: Alta, just hold on a second.

PROFESSOR CHARO: Okay.

DR. SHAPIRO: Eric?

DR. CASSELL: I do not want to impugn the motives of the pediatric or any other oncologist either in trials. Obviously the best for those patients is desired but there are two differences between a research setting and the ordinary clinical treatment setting.

One of them is the primary responsibility of the researcher, I hope, is to the outcome of the trial because that is where the knowledge comes. And if there is a conflict between a good trial where good knowledge will come and the good of an individual patient, there should be a conflict. If there is no conflict, then somebody is not doing research properly on the one hand. And on the other hand -- I will be glad to clarify that but so will everybody else. On the other hand, there is the

other problem about protocol violations. Mostly we do not bump people off ordinary treatment when they violate treatment. We may adapt our treatment to them and so forth and that, I hope, is not true of most of your trials. There are differences between a trial and ordinary treatment.

You can be so involved in trials and do nothing else that it does not look like there is, but in point of fact there is (1) the conflict of interest within the individual and (2) the difference between the patient in that and the patient in ordinary treatment.

DR. SHAPIRO: Thank you.

Bernie?

DR. LO: Alta first.

DR. SHAPIRO: Oh, Alta, you are next line. I forgot. You are far away. I cannot see you.

PROFESSOR CHARO: It is okay. Actually this follows directly on Eric's comment. When I listened to Dr. Murphy's presentation I was struck --

DR. SHAPIRO: Hold on a second, Alta. Can you hear this? Okay. We can hear you. Thank you.

PROFESSOR CHARO: Okay. When I listened to Dr. Murphy's presentation in particular I was struck by the absence of the things Eric talked about and also an awareness of the degree to which research

requires some lack of individualized attention to patients. One randomizes them among various dose levels, for example, or other details of a treatment regimen and the goal is to keep them on the particular study arm that they have been assigned to until there is strong reason to take them off. Whereas, in an ordinary treatment setting out of the research setting you would manipulate their treatment much more readily. Although I recognize that you might still wind up giving somebody what is equivalent to a best guess, it does lack the kind of individualized attention that is one of the hallmarks of the doctor-patient relationship.

I find myself thinking that it justifies a degree of scrutiny.

DR. SHAPIRO: What was the last phrase she said?

DR. MESLIN: Degree of scrutiny.

DR. SHAPIRO: A degree of scrutiny was the last few words.

PROFESSOR CHARO: That is correct.

DR. SHAPIRO: Is that right, Alta?

PROFESSOR CHARO: Yes.

DR. MURPHY: I feel that I have to just comment both to Dr. Cassell and to Dr. -- who is the phone speaker?

DR. SHAPIRO: Charo.

DR. MURPHY: Charo.

PROFESSOR CHARO: The mystery woman.

DR. MURPHY: The mystery woman voice. About the quality, I think, that we all strive for as both treating physicians and investigators, and that is to maintain ethical equipoise with regard to the individual child subject. Because, Dr. Cassell, you were referring to two different differences between a trial and a treatment. One being that the investigator is related to the -- is more committed to the outcome of the trial. You hope that -- just seeing it conducted correctly.

DR. CASSELL: The hope that the investigator is more committed to a correct trial and good knowledge.

DR. MURPHY: Right.

DR. CASSELL: Investigator is committed to knowledge. That is what the scientific -- more that the investigator is committed to that individual patient's best interests.

DR. MURPHY: However, let me clarify that if you are doing a randomized trial --

DR. CASSELL: Yes.

DR. MURPHY: -- and you have this quality of ethical equipoise which we do have knowing how it is set up and that we -- there is uncertainty in medicine, we do not know which arm is better a

priori. That is why we do the trial, so I have no problem in both offering both arms of a randomized trial and maintaining the role of the treating physician in equipoise.

DR. CASSELL: No one has any argument with that. You could not be more correct but that is not what I am saying. Equipoise is not what we are talking about. We hear as a particular there is a classic 20th patient instance in which 19 patients have failed the trial, but until 20 patients are enrolled it will not be statistical, this and that.

Mostly you -- that 20th patient should be enrolled and mostly to get that patient enrolled we do not tell the patient "19 patients have failed this trial, you are the 20th patient." We want the patient to be enrolled. Otherwise the trial is not going to be a trial. It is a classic -- it is used again and again as an example.

The important thing is that if you do not finish that trial, then all the 19 patients before were used to no purpose. And there is a dedication -- not equipoise. Equipoise is not the issue. It is where is your primary responsibility to the knowledge produced by the trial, which involves a number of people, and to an individual patient. And that is a conflict of interest that we did not invent today, I promise you. And that is very,

very seldom understood by oncologists particularly.

DR. MURPHY: Thank you for that lecture.

DR. CASSELL: No, no, do not worry about lectures. They do not hurt you. On the other hand there is this: Why oncologists particularly? Because you do have the expertise and most of the patients are enrolled and so it is not like somebody treating heart failure where lots of people treat heart failure. You are the ones who know more. That is why it is particularly important for oncologists to know.

DR. SHAPIRO: Bernie?

DR. LO: I want to shift gears a bit and ask Dr. Farley a question. You explained to us how you do epidemiologic research and particularly a sort of research on enhanced surveillance on conditions that are often reportable by state law in the first place.

I want to ask you to expand or to say a little more about the expertise that some of the IRBs you deal with bring to the review of epidemiologic research, as opposed to clinical trials, or other types of research that are probably more common.

You talked a lot about the kind of delays you face in kind of getting multiple IRB approvals for studies that need to be done in a very timely

fashion because of disease epidemiology, but could you say a little bit about whether you feel that IRBs that you go before really understand the kind of work you do? Are they applying concepts that really are meant to apply or fit best for other types of research? Do they understand the kinds of subtleties or not so subtleties about how consent may take on a very different meaning in the situation where the disease is reportable?

Just to put it in context, we have struggled here with the notion that both the regulations and sort of IRB experience often is geared to a certain type of biomedical research and other types of studies that do not fit that sort of template and may not get appropriate attention.

DR. FARLEY: Well, that is my feeling on the subject and I have to say having dealt with the three different IRBs fairly routinely that the university based IRB is the one that was least prepared to deal with our proposals when we first started doing this research and I think there has been kind of an -- in some ways an education process that they have learned through the years more about what we do because we have a fair number. The volume has continued and increased over the years but very much the initial stages of the evaluation have been trying to make it like a clinical trial at

the university level because that is what they are seeing most routinely coming through.

CDC's IRB has become more and more active, as all IRBs. They are all kind of revving up to a higher level of attentiveness as this is being viewed very carefully and closely and the CDC's IRB is probably the most expert one of the three we are sending it through.

I do have to say that the state health department's IRB brings a third perspective and I am not arguing for the need for this thorough review at three different places, but there are perspectives that are brought from the public health sector in the field versus centrally at CDC that sometimes come to bear on the issues of the evaluation, but my impression has been that the university has been the least prepared to deal with the epidemiologic research.

DR. LO: If I could follow up. Could you please give us an example of how the state department and CDC provides an insight that either the CDC -- I am sorry, the IRB from the state public health department brings insight that the CDC board or the university board may have missed and enhanced the sort of protection of subjects or strengthened the protocol in some way?

DR. FARLEY: Well, whether it protected the

subjects anymore could be argued, but an example would be that the CDC -- for instance, a protocol that had to do with reviewing cases of an opportunistic infection that was fairly closely linked to patients with HIV disease. The case report form included the -- a list of underlying diseases that may predispose to the particular invasive infection and it included a check-off for HIV.

In the State of Georgia reporting -- and so we were using this form that would be distributed to labs throughout the surveillance area in the State of Georgia, only AIDS is reportable by name, HIV infection is reportable but not by name. And -- but in other states HIV may be reportable by name.

And so they were looking at the -- if this form was coming out looking like a request from the state health department to check off on this case report form that the patient was HIV infected, that it was not in compliance with the state regulations in terms of -- we had to change the wording to indicate that this was an optional process and that only AIDS was reportable by name.

So was that patient more protected? I could argue that no. I mean, we were going to protect the confidentiality. No identifiers were going to accompany this data ultimately to CDC.

None would go out in publication.

To me there were regulatory issues being addressed there, but was the human subject more protected? I am just not sure.

DR. SHAPIRO: Thank you. Do you have another question, Bernie?

DR. LO: Can I just follow up because the reason I want to pursue this -- I mean, we hear or at least I hear very broad statements all the time about sort of the value of local IRBs or things like that and I am always trying to sort of get specific examples that go beyond the level of "we are more in tune with local values and, therefore, we do a better job."

But if I could push a minute on -- or find out more about this particular incident, one other interpretation without my knowing, you know, all the facts to the case is that confidentiality of HIV status is a large concern and was there the possibility of designing the study so that even when you got the primary data from the initial surveillance report it was presented to you in a coded fashion so that you could have gotten the HIV information, but using an identifier that was so scrambled that it would be very hard to back track and identify the individual?

DR. FARLEY: Well, actually in this case it

had actually been approved by -- the acquisition of those data had been approved by the Emory IRB, our university based IRB, but it was called into question by the state. And, in fact, what we did was to develop a process that would strip that identifier or that data point from the information that was passed on then to the state health department so that they never were in receipt of that information by patient and so, yes, we did incorporate that but it still meant that we as the university based investigators are still, in fact, collecting that information and we are protecting the confidentiality and none of the names are -- all of the personal identifiers are stripped from the dataset before it goes to CDC, but in this case we added an extra layer of stripping between the university and the health department.

DR. SHAPIRO: Thank you. Maybe we will take one more question because I think we have to wind up. Steve, do you have a question?

MR. HOLTZMAN: It is a question of Dr. Cassell. I will do it afterwards.

DR. SHAPIRO: I see. Well, all right then. Let me then thank our panelists very much for your very thoughtful remarks and, indeed, very stimulating remarks. We really very much appreciate once again that you have taken your time to be here.

Thank you all very much.

Unless there is some reason not to, we are going to adjourn. We are adjourned.

(Whereupon, at 3:32 p.m., the proceedings were adjourned.)

*** * * ***