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I N D E X

P R O C E E D I N G S

OPENING REMARKS

HAROLD T. SHAPIRO, Ph.D.

DR. SHAPIRO: As you recall, our agenda this morning is primarily focused around two panels.

One panel representing in some sense -- I do not mean that we have elected representatives and so on -- but at least representative of pharmaceutical and biotechnology companies and one that deals with research firms that are heavily involved in this area.

First of all, I would like to begin by welcoming our guests. We very much appreciate all of you being here today and we know that this is a considerable effort on your part and time taken out from busy -- other busy things you have to do and we are very, very appreciative of you being here today.

I think, as all of you know, we -- one of the efforts we are in the midst of is evaluating in broad but we hope effective terms the general oversight mechanism in this country for the protection of human subjects. I mean, I do not need to tell you what that system is. It is just that it has been in place for roughly -- well, for quite a long time now depending on which date you take as a starting point.

And we have been asked by the representatives

of the President and so on to take a -- to review that to see if it is still serving the country well and whether there are any alterations, suggestions and amendments that we might recommend at the end of our study.

We hope that this study will be completed roughly around the turn of the year. That is our objective now and we seem to be on track.

And we have decided that we would look not only at the protection of human subjects that somehow fall under the current oversight mechanism but whether there are human subjects elsewhere in this country who somehow fall outside that oversight system and should perhaps be made part of it. This is one of the things that we are considering.

And so we are very grateful that you have come here today because together, both individually and together, you represent very important parts of the system of biomedical research where human subjects may be involved at least in some of the work that you are involved in.

And so we are really looking for some help and some insight to decide -- just help us inform better as to what we should think about and what we ought to be concerned with, with respect to assuring that human

subjects get appropriate level of protection without trying to close down or in any way inhibit very important research from going on.

Now some time ago, I cannot remember the exact date, NBAC, in fact, adopted a resolution that all Americans who -- and I will just paraphrase it. I do not mean to be repeating it exactly -- who serve and participate as subjects in medical experiments ought to somehow receive the twin protections of informed consent and independent review. That, of course, occurs in -- already in a good deal but not all of the research involving human subjects so that is one of the areas that we are interested in and trying to investigate what, if any, changes we ought to recommend in federal regulations in this respect.

So as, I think, commissioners know, this is -- today's session is organized as a panel and a conversation between ourselves and our guests. While I certainly will allow our guests to have -- say anything they would like to, to begin with, that is not necessary. We were not expecting -- they were not expected to do that, I think.

I think we just want to start right off into questions but I would really invite our guests at any time if there is something they want to say that is not

in direct response to a question but you want to put that issue before us, you are more than welcome to do it because we may or may not hit on issues which you think are really quite important and which you want us to consider.

Only one logistical issue and then we will start off. If you want to speak and be heard just press this button in front and the red light will go on. Then you are ready. And when you are finished if you would turn it off that sort of makes the sound system work reasonably well.

Now let me start off by just asking the question which I really referred to a moment ago and then see what responses you may wish to offer and then we will see what other commissioners might have in their mind.

As I said, there are human subjects protections in place for an awful lot of research in this country but on the other hand there is research that is going on that is not covered by current federal regulations. If research is not involved in the FDA process and it is not financed by the Federal Government there are really no regulations that apply.

I guess the issue is, is this an issue? Is this a problem? And if it is a problem, should

anything be done about it? I do not know who wants to address that issue first.

Yes, Bert?

ETHICAL AND POLICY ISSUES IN THE OVERSIGHT OF HUMAN SUBJECTS

PANEL I: PRIVATE SECTOR ROUNDTABLE

PHARMACEUTICAL AND BIOTECHNOLOGY COMPANIES

DR. SPILKER: Thank you, Dr. Shapiro. It certainly is a pleasure to be here today and thank you for the invitation.

The pharmaceutical industry, in general, and in particular and specifically, does go through IRBs for literally all of the intervention studies involving human subjects so we believe that there is not a category of intervention studies that we are not using IRBs even in situations where it is not required to do so.

However, in observational research, particularly studies where archived data or tissue samples are used, the majority of those studies also go through IRBs but I would not say that every one of those studies does but we believe the system is working well, that we are actively participating in following all the rules of the system.

I think some of the issues which you may get

to later, and I will not go into it now, may have to do with work load of the IRBs and how that can be addressed.

DR. SHAPIRO: Can you please say a word, so I will just understand better, what you refer to as observational studies as opposed to the tissue studies or the others?

DR. SPILKER: Well, observational studies are a very broad category. It certainly would involve or could involve a lot of epidemiological or pharmacoepidemiological studies in large multipurpose linked automated databases which I know do go through IRBs before those are conducted.

The studies that I was referring to where you get into a little bit more gray area where a study has already been completed, and a number of years later a question arises and people want to go back to the data to address that question. Well, I think if you have to get archived tissue samples that are at an institution that conducted the trial you probably would -- and I think in all cases -- go through the IRB again and tell them that, yes, we now want to go back and look at these archived samples. But if you just have some data in your own labs you might -- or offices, you might not go to an IRB just for a look to address a

single question.

DR. SHAPIRO: Thank you.

Yes?

DR. WANLESS: I would just like to concur with Dr. Spilker. At Bristol-Myers Squibb we ensure that IRB approval is obtained for all studies in which we are involved and that also applies to any collaborations we have with external institutions or academic institutions and, indeed, we apply the same standards not only in the United States but to all of our international research. We ensure that all of the necessary protection is taken exactly as though the study was being performed in the United States.

DR. SNIPES: I do not mean to be redundant but Glaxo Wellcome policy is consistent with that that has been outlined by my two colleagues.

DR. SHAPIRO: Thank you. The same experience?

DR. WELLES: Yes. We have had had the same experience. I just would like to amplify on one point that Dr. Spilker had made and that is the difficulties of archived biological specimens and in a number of cases other important research questions have come up and we have had banked even plasma samples and we have applied the regulations very strictly and not been able to go back and do further assays unless the informed

consent from a particular site specifically said so and that has been unfortunate in some instances.

So you are sort of left with the issue of either providing informed consent that is very all encompassing and vague, which we do not like to do, or not doing the research we would like to do sort of after the fact.

DR. SHAPIRO: Bernie?

DR. LO: I want to first echo Dr. Shapiro's thanks to you for coming and helping us think through some difficult issues. To follow up on your comments about IRBs, one of the criticisms of IRBs is that they are overwhelmed with too many studies to look at.

They do not have the resources to have the kind of personnel and other support they need to do their job and it takes way too long to get approvals, thereby delaying research. I was wondering if you could comment from your perspectives in the private sector on those issues.

How long does it typically take for an IRB to review various studies in your organizations?

What kind of resources go into the IRB? Is the chairman paid?

Is there line support to support the IRB?

And what suggestions can you make for sort of

streamlining the IRB process so it does the job of protecting human subjects but does not impose undue delays or burdens on important research?

I have a sense that you may have figured some things out because of your concern for being efficient that may not be standard practice, for example, in the university IRBs.

DR. SHAPIRO: Dr. Spilker, I know this is something you have thought about so I am going to turn to you first.

DR. SPILKER: Yes. I think Dr. Lo has gone right to the heart of the issue here in these matters. You have asked several questions and I will try to comment on some.

Number one, I would imagine that the group is well aware that many IRBs are charging for reviews and those fees vary a great deal but the average fees are maybe a $1,000 per review. It is hard to know. I never really did a survey of that but that is an impression that we have. So that is primarily to pay administrative staff to help them because without administrative staff, given the large numbers of protocols and informed consent and other documents, and periodic reports they have to review that would be extraordinarily difficult to do.

The industry sees the wisdom in that.

I think some groups apply it primarily to sponsored trials and not to trials submitted by academics but I think there must be a lot of variation in that among institutions.

Another point you were asking about has to do with the work load. Well, we do think the system is working well. It is being burdened by an incredible work load, not just by certainly industry trials but by all trials in general.

The number one approach that industry has felt would reduce the work load -- we are not talking about the training of them and all the other things that were in the IG report and have value and which we support, and we do support many of the recommendations in that document -- but in terms of reducing their work load the -- if there was a possibility of having a central IRB not at all in the U.K. sense of the term but a central IRB that would be able to reduce multi-center trials and this would be accepted by the local IRB, never forced on them but voluntarily accepted by them, which means that some of those in a trial might accept it and some would not, over a period of time probably in conjunction with development of accreditation of IRBs so that an IRB would be more comfortable and trust

results of certain IRBs that their judgments would be able to be accepted in terms of conducting an expedited review rather than a full review.

I would imagine that a large percent of the trials looked at by a local IRB could be eliminated. I think that everyone realizes that when you look at the government's five cancer cooperative groups, the ECOG, SWOG, POG, you know, they -- if they are going to do 200 sites they are going to have 200 IRBs look at this. Now that is patently absurd in my view and I think in many other people's views.

Now we do know that the NCI is going to be conducting a pilot study starting this summer, hopefully, at which they are going to be exploring this concept particularly for these cancer groups but I think that the same principle certainly applies to all others.

Now we did prepare a white paper, which I know has been distributed -- thank you, Eric, for doing so -- to the members so I will not go into many more details and even that does not totally address the issue.

Now the industry asked for and received a meeting with OPRR and FDA, which was held last December 14th, to address this issue that was set out in the

white paper and we are working with both groups trying to create -- well, with FDA in particular -- to create a series of principles that they would be able to endorse. This would not require changing laws or regulations. And with OPRR to pull together the different aspects related to this.

We believe that if this information was more widely known to and became known to the local IRBs it will certainly take time, there will be a lot of questions, there may be a lot of skepticism in some areas, but I think that over time it will gradually increase and improve the situation.

Dr. Lo, you asked about how long does it take. Well, the only answer that I know is too long because some -- many institutions, number one, have policies they will not even take a protocol to an IRB until a contract is signed between the institution and the sponsor. That sometimes takes a long time. Some IRBs do not meet very often. More institutions are having multiple IRBs formed so that they can basically stagger their meetings and meet more frequently but I do not think that those -- some of those are getting to the heart of the problem.

I think the real heart of the problem is how do you decrease the work load and bring it a bit more

under control.

DR. SHAPIRO: Thank you.

DR. SPILKER: Especially where it is redundant.

DR. SHAPIRO: Do any other members of the panel want to address this particular issue?

DR. WELLES: Yes. I would like to start with the timing of review and in our experience it has been highly variable and, to concur with Dr. Spilker, we often have studies that have multiple sites. For example, in my group now there is a study that has 85 sites. GenenTech as a corporation has run some very large cardiovascular trials with 15,000 patients so you can just imagine how many sites might be involved with that and that really creates a lot of difficulties for us to get our studies up and running.

And just as another example, within my group there is a Phase I-A study and we have had one IRB that has not responded fully by six months.

So I would say for the academic IRBs the range of time would be one month at the very least and that would be unusual and it is up to six months and typically can be three to four months.

In terms of our own budgeting for IRB review it generally costs us -- I think we allocate about 500

and use that as an average so it could be nothing and it could be up to $1,000.

And to deal with these difficulties we are attempting now more and more to go to commercial IRBs and have as many of our sites that can utilize a commercial IRB do so, so that at least we can sort of turn the key on a number of sites and I would have to say that just qualitatively I have not noted any great differences in terms of the vigilance about safety issues between either the academic or their commercial IRBs.

DR. SHAPIRO: Thank you.

Yes, Dr. Snipes?

DR. SNIPES: It is going to be again a bit of redundancy but I would just like to reiterate that the major problem is the work load and the time to review protocols and when I am designing a trial I usually use an average of eight weeks in the IRB approval process, and that is sort of the minimum just because if you do not get the timing right you will have to wait until they meet again and they may already -- you have to have a month in advance and getting the materials to them.

So basically if you miss the meeting you are at least two months away, particularly with the

academic IRBs, of actually getting the review.

And you realize this is just the first time around. If there is an amendment to the protocol or some safety material you want them to review -- during the course of a three year trial you may add up to six to seven months in IRB approval.

And again over my 13 years, I started out with no such thing as IRB fees and now they average -- I am sort of in between the two figures you have heard just because of a recent trial -- about $800 and that is just part of the standard budget that the investigators put forth.

DR. SHAPIRO: Any comments?

DR. WANLESS: It might be worth just pointing out for the sake of comparison that actually in terms of efficiency the U.S. is probably way ahead of everybody else. Most countries are less efficient but on the other hand just to pick up on one of Dr. Spilker's points, there is in one or two countries this concept of a central IRB whose opinion will then be accepted by all of the other ones and I think if it is correctly regulated that is an ideal situation.

DR. SHAPIRO: Thank you.

Alta?

PROF. CHARO: Thank you. I would like to

continue the discussion about ways to manage the problem of collaborative research, which we all recognize as being an enormous burden, and maybe urge -- maybe ask if you could perhaps get a little bit more specific about some of the proposals that you are considering.

Some of the problems that have been referred to in the papers we have received have been differences in the language of consent forms, and most of us would recognize that often that is really a matter of style rather than substance.

In my experience, though, there have been other times where there have been disagreements that are far more substantive. One, for example, would be one that might look technical but actually often has a substantive content and that is compensation clauses in which there is disagreement about the language that is going to be used with regard to promises to subjects in case of injury.

Interestingly enough, the promises are often more extensive in my experience by the pharmaceutical sponsors than they are by the academic centers, which tend to be more conservative about saying we may not cover your injuries.

And in my experience that has often become

such a sticking point that the entire collaboration has been at risk over the negotiation about the language and it has been particularly difficult in multi-center research in which there has been concern by the sponsor that varying language at the different sites creates yet another level of legal vulnerability.

More clearly substantive have been questions such as the inclusion of women prior to the statements of policy at the federal level in which some academic centers wanted much more aggressively to include women at fertile years in their research but the pharmaceutical sponsors were much more reluctant to include them. Something which can be documented empirically.

More recently issues about the replication of old studies that took place with single race groupings in which the effort is simply to see whether or not one can replicate the data in a different context but in today's milieu perhaps it is medically and/or politically inappropriate.

When you have got these kinds of differences, which go beyond questions of style in the consent form, and where mere accreditation for competence does not necessarily answer the question of what is the wisest course of action, can you describe what you are

contemplating at this moment as the range of possible solutions to a central kind of streamlined guidance that people can all buy into to substitute for this kind of localized review?

DR. SHAPIRO: Dr. Spilker?

DR. SPILKER: Well, I congratulate you in asking about eight or ten very involved questions. I will do my best.

DR. SHAPIRO: Well, someone made a new record yesterday with 24 questions.

(Laughter.)

DR. SHAPIRO: I will not say who it was.

DR. SPILKER: The first comment is that as we envision this central IRB review it does not have -- say they review a protocol and informed consent -- and we are saying that any one of these sites -- say there are 200 sites in a trial, any one of them could be asked to be the central one. It does not have to be a new -- and we are not talking about anything new. You do not need any new laws, no new IRBs, and actually precedent exists, compassionate plea protocols often go through central IRBs, treatment INDs are almost always going through -- they are sometimes called national IRBs. They have other names but this concept is not new. It is not unique. That is the first point.

There is precedent and especially with treatment INDs.

The point is they might approve something so the local IRB gets this approval. They may say we will accept the approval of the protocol but we want to look at (a) the informed consent and we are not going to accept that because at our institution we want something else.

It has not been my experience, and I defer to my colleagues here to point out some exceptions if they know of any, and it might be, where having different informed consents at different institutions is an issue. I think the informed consents can differ and do differ in most of the trials where the protocol is identical and they differ because the members of the IRB have different views as to the language, the contents, the disclosure, and the amount, and all these things, and that is legitimate.

My point is this: You will still reduce the work load if you have say 150 out of 200 local IRBs accept the protocol and 100 of those not accept the informed consent and go over that. It still can make it -- I am talking about the whole system -- a lot more efficient.

So you do not have -- now you raised also the issue, which I totally agree with, the fact that the

IRBs should be looking over not only the financial aspects that they deem relevant to look over but also advertisements that are going to be used.

Now they can be used -- looked at by a central one but it is certainly within the purview of the local IRB to say we want to look over these financial arrangements that you have at our institution and this is our view, et cetera. So what I am describing is something that does not have to be all or none, that the local IRB has to buy into everything.

Now you raised the question of women of child bearing potential. I would say the industry is very proud of the fact that even though the pendulum in society has gone from one extreme to the other, and I was amazed at how far it went.

That we, I think, are being far more responsible by saying, "Look, women who are pregnant should not be getting new drugs in Phase II when their efficacy and safety is still being evaluated." We do not really even know about the drug, let alone to put them into trials and we want to make sure -- get a lot more data and have a lot more assurance before we will let them in trials. I think we are acting responsibly, ethically and appropriately in those areas.

You then raised the question of race. Well, I was with a group yesterday that was with the Black Medical Association trying to figure out how in the world they can try to enroll more Blacks into clinical trials when there is a lot of resistance in that community to doing so. My point is this:

That there are a lot of companies, organizations and others looking into this trying to enroll and Blacks are not the only minority. You have Hispanics who have different cultural images and activities and feelings. And sometimes it is religion, sometimes it is culture, sometimes it is other things.

But the industry is not necessarily -- I think sometimes people look at the industry and say, "Why haven't you done this," when the investigator is unable to enroll those patients.

PROF. CHARO: Dr. Spilker, I must have misspoken because my goal here was not to attack the positions of the industry. It was simply to ask how one handles the integration of multiple IRBs with different attitudes especially in light of the comment in the white paper that the market will operate -- might operate to exclude centers that do not collaborate in the integration of these provisions.

DR. SPILKER: I am sorry if I misunderstood

your comments. I would say the industry recognizes the importance of these minority groups and is taking steps and sometimes realizing you cannot just try to go to certain communities and bring people in but you want to go to maybe enroll more, as an example, Black physicians into conducting clinical trials to make them more knowledgeable.

I would say the FDA has, in my view, a wonderful attitude towards -- it is not just based on race and gender but also age. They say we want to look -- have the company stratify their data and analyze it based on those criteria and if there is no -- if anything comes out, yes, do a separate study in the aged; yes, do a separate study in women but for many diseases there is no reason to do so.

So I think we have an appropriate balance right now.

DR. SNIPES: I think along the same lines of the last aspect of that question regarding minorities and women. The fact that the FDA does ask in looking at data to analyze it along those strata in terms of safety and response has certainly raised the sensitivity within industry, specifically Glaxo Wellcome.

We actually have a group that is organized to

look at a policy in terms of inclusion of women into clinical trials, which has come about in the last three years. The whole point is to raise the sensitivity. I think we are getting more women in clinical trials. In fact, we are beginning to have only women clinical trials based on just some of our research.

But the issue is it is not an exclusion anymore. You have to have a rationale for why you are not including women and I think we have alluded to sometimes it is not the right thing to do because of the risk of pregnancy or lactation but normally you can bring women into trials earlier.

We are bringing women into trials earlier. We are putting urinary pregnancy tests early in the exclusion/inclusion criteria because now that you can do HCG urinary tests versus doing serum tests as we did ten years ago, you can actually get a pretty rapid read whether or not a woman is pregnant. Then you have to look at the protocol and see what the duration is, et cetera, but we are putting in those pregnancy tests frequently in our trials.

In terms of minorities, it is still a challenge for all of us and the industry as well, and I think what we have tried to do or are trying to do is a multifaceted approach to including minorities. One is

to go where minorities are. Yes, you have to go to the academic centers. You have to go to the investigators but you also have to get advocacy groups within communities, churches, whatever, where you have to first educate about the disease, the ramifications of the disease, and any potential benefit it might be to participate in a clinical trial.

We are still living under the old Tuskegee realm, too, in terms of fear of clinical trials so it is still an ongoing -- I think it is an uphill battle but I think education is helping in it and industry or at Glaxo we try to be proactive in saying how -- based on the population and the prevalence of the disease how many minorities would you expect to be in it. And that could be Hispanic depending on the disease prevalence.

And keeping a track in a database of how many women or minorities are actually being enrolled in these trials and then putting provisions in the protocols or in the clinical design to try to enhance recruitment if we are not living up to the population prevalence or the disease prevalence.

DR. SHAPIRO: Could I just ask a clarifying a question on this issue and then I want to go to Larry. You are next on the list here.

I am not trying to ask a question about the policy or the justice issues involved here at all, although those are important issues but that is not the source of my question.

My source is -- my concern or question is that if you do have these, as you point out, a central IRB, whatever name we give it, which a local IRB can either accept or not accept as you have -- as Dr. Spilker has suggested. It sounds like a reasonable way to proceed but one IRB of this 100 or two or half a dozen really want the trial to have some different way of selecting patients. The other 144 do not require that.

Is that a problem for the trials as you -- that you might -- or not? I mean, how -- what would you do with that issue? Maybe it is not a problem. I just do not -- I am just asking a question.

DR. SPILKER: I believe today the sponsor has a choice.

DR. SHAPIRO: Right.

DR. SPILKER: The sponsor can say these two IRBs feel differently. We will, therefore, do a separate study at those two institutions and we will give a different protocol number. Let them go off and do a separate study.

Another option is it can say, well, we

understand you have strong feelings. We will have to decline your participation. That does happen.

Both those examples happen and there are other opportunities.

Another third option is if they wanted something in addition to what was in the trial rather than changing the trial that can often be accommodated by saying, well, at those two institutions they will also do additional tests or studies that are -- you might say an appendix, if you will, to the protocol, and that is accepted as well.

DR. SHAPIRO: Thank you. That is very helpful.

DR. WANLESS: Could I just add --

DR. SHAPIRO: Yes.

DR. WANLESS: -- just to pick up on this last point. I think it depends on the stage of the trial. If it is an early trial where you need to have very rigid entry criteria and so on that has to be maintained. But if it is in later phase trials certain flexibility is probably preferable because that is closer to the real life clinical situation and I think we can accommodate that type of flexibility.

DR. SHAPIRO: Thank you. That is very helpful.

Larry, let me go to your question. You have been waiting patiently.

DR. MIIKE: Not to worry. I can only ask two questions at a time.

(Laughter.)

DR. MIIKE: The first one really does not -- I do not need a response from you if you agree with what I am saying. I am just trying to paraphrase what was said initially by all of you. And basically it is this, is that even though you are not subject to the Federal Common Rule, the partners that you routinely engage in research in and testing are, and have voluntarily extended that to these activities. And then on top of that the FDA process does require some human oversight, and that is the way that folks go.

So in practice you are subject to those rules except for those examples that you mentioned.

I have a specific question for Dr. Welles. In the beginning you mentioned something about archived tissues and every once in a while you get to a situation where you just cannot do the research because -- is that because of the institution that is holding the tissue and they have some objections or some -- it seems to me that it is not an insurmountable problem and it seems to me it is more a misinterpretation of

what is allowed on the rule. So can you expand a bit on that?

DR. WELLES: Well, the example that I cited was a few cases in which we have actually held plasma samples in our own freezers and wanted to go back and do assays on those samples. Went back and pulled the informed consent forms and realized that they were not worded in a way that would enable us to do additional assays.

So when we outline the study to the patient we actually say your blood will be drawn for, you know, routine chemistries, et cetera, et cetera, and if the specific test was not mentioned we would not feel comfortable doing the additional assays.

We would have to go back and reconsent that patient and often it is impossible to find them.

DR. MIIKE: But I believe the rules allow you that if it is a minimal risk study that is exactly an area in which -- and there are waivers for consent and so -- because, you know, you have actually asked the subject for more informed consent. That is what is usually routinely asked for in a surgical specimen and those kinds of things could always --

DR. WELLES: I guess --

DR. MIIKE: So it may be just a part of your

being extra careful --

DR. WELLES: Exactly. I guess what I wanted to sort of suggest is that we take a highly conservative approach to the protection of subjects so we would never do those assays in the absence of specific consent and the patient knowing about it.

DR. SHAPIRO: Dr. Spilker?

DR. SPILKER: I would like to expand on that answer a bit if I might. One of the major fears of the pharmaceutical industry is that some of the laws being proposed in congress on data privacy are going to be prevent this type of research exactly and the reason is that if you want to go back and get an informed consent of the patient, and say there are 100 patients in that trial, even if that trial was to finish last week, when you go back some of those patients will have moved, some of them will have -- I mean, hopefully, say last year -- some may have died, some are going to be impossible to find or to even explain it and get their informed consent.

And I am certain that everyone in this room appreciates that if you get the informed consent of 80 patients out of that 100 you cannot do that trial no matter what you want because you have a biased sample and you can now not say we have taken these data from

100 or 80 of the 100 who were in the trial. I mean, because your results are going to be seriously, and correctly, questioned by anyone looking at that.

So, therefore, what we want to ensure is that we are not prevented from doing research because you cannot go back to patients to get informed consent when the type of study you are going to be doing is of minimal risk or could not -- but still that study should be approved by the IRB.

We are saying that an IRB or ethics committee can deal with it; can say, yes, this study is reasonable; yes, you can go back and do that study.

DR. MIIKE: All I am saying is under the current rules that you would be able to do it.

DR. SPILKER: That is correct and we are concerned about changes that would make that difficult.

You know, I do want to say that we do consider that we are working under the Common Rule in regard to your first point. I mean, some of the final -- I am not an attorney so whether it is directly or indirectly as you were describing, I am not 100 percent sure, but we certainly say, yes, we are working under the Common Rule.

DR. MIIKE: Just a follow-up question. I am

also assuming --

DR. SHAPIRO: This is the third question, Larry.

DR. MIIKE: Okay.

(Laughter.)

DR. SHAPIRO: Only one next time.

DR. MIIKE: I am learning. I have not gotten up to 24 yet but I am learning.

I am also assuming that when you talk about IRBs you are talking -- you are routinely talking about your partner's IRBs. All of the tenor of the discussion has been that it is not that you have IRBs yourselves, it is the institutions that you are working with.

DR. SPILKER: That is correct. There are a few cases where pharmaceutical companies may have a Phase I unit themselves and will have established one. Those are exceptions. There are a few cases where investigators are really people working in a pharmaceutical company. That is pretty rare but I would say 98 percent of what we are speaking about are the academic or other institutional IRBs.

DR. SHAPIRO: Steve, let's go to you.

MR. HOLTZMAN: First, thanks for coming. Do I have to go through all of my conflicts of interest with

these organizations?

DR. SHAPIRO: No. Save us.

MR. HOLTZMAN: Okay.

(Laughter.)

DR. SHAPIRO: We know who you are.

(Laughter.)

MR. HOLTZMAN: I will let that pass.

(Laughter.)

MR. HOLTZMAN: I want to come back to Larry's question and get out of the pragmatics and up to a level of principle because the way Larry represented that first statement, do you agree, was industry conforms with the principles of the Belmont Report and the principles of the Common Rule because we have to because the institutions we work with have to.

And I think, therefore, it raises a view of industry under the current regime where there is the possibility that we have of not working under those strictures, that we want to stay outside of those strictures.

With the result that you get this sense that I have certainly had as I sit with my colleagues here of saying, why on earth does it matter where the money came from of whether or not the subject of an experiment deserves the protections so my question is

the following:

Allowing for the fact that people of good faith can disagree about what should be the scope of what is human subjects research, questions about whether a coded sample should be considered versus an anonymous sample. Let's bracket that question for a second.

Given the pragmatic fact that with paradigmatic human research, subjects research, we essentially do fall under the Common Rule or the FDA, for the -- for a variety of pragmatic reasons, and given the in principle reasons why we ought to, what stops us as an industry from embracing an expansion of human subjects protections effectively that says it does not matter where the money came from, they should apply.

DR. SHAPIRO: Press your light so we will all hear you.

DR. SPILKER: I agree. If you are talking about the extension of the Common Rule, if the Common Rule were to be extended as it is currently written and interpreted, I believe the industry would like to see the specific wording to see whether or not there were any implications for the industry.

I can imagine a scenario where there might be

some issues and we would like to adjust the wording. The principle, I do not think is a problem.

MR. HOLTZMAN: I want to jump in there because I think that is an important distinction. People of good faith, both in -- not industry versus nonindustry but in general about -- and we have disagreed here of what is human subjects research. That is the breadth of the protection. That is distinct from whether once you have come to an agreed upon breadth than that should apply regardless of the source of the money.

I think what I am hearing you saying is if we could come to reasonable agreement on the breadth we would have no problem as an industry.

DR. SPILKER: I agree with what you just said.

DR. SHAPIRO: Is there a general agreement from the perspectives of the various people and Panel I has already spoken, I think, quickly and efficiently. Thank you.

(Laughter.)

DR. SNIPES: I would agree. I agree. I just think it has to be carefully analyzed and justified as we do it but in essence and philosophy I agree.

DR. WELLES: Yes, I would agree as well. I guess getting then further into the definitions is another matter.

DR. SHAPIRO: Thank you. Eric, you are on the list. Diane, you are next. Yes, Diane?

DR. SCOTT-JONES: I have three questions if that is okay. First, I would like to hear --

DR. SHAPIRO: That is down from the 24 of yesterday.

(Laughter.)

DR. SCOTT-JONES: First, I would like to hear you say a little bit more about local standards in the review of research. You have said that some differences from site to site in large multi-site studies are fine, such as minor differences in language for the consent forms, but I would like to hear you say a little bit about the value that you place on the importance of local standards in the communities that would be involved in multi-site studies, especially the value you would place on that in relation to the value you would place on uniformity.

And then the second question I have is about the composition of commercial IRBs. Coming from academia, I do not know very much about commercial IRBs and I would like to know if you are satisfied with the composition of them. Do they have adequate community representation, for example? Do they have adequate representation of different population groups?

And then my final question has to do with the point that you have made about waiting for IRB review and certainly I get annoyed with our IRB at my university because of having to wait and then having to make minor changes and waiting again. I am wondering what alternative you see to that. How could you avoid some of that waiting to get on a schedule and to get your protocols reviewed? What would yo do instead?

DR. SHAPIRO: Thank you. Who wants to go first? Dr. Spilker again. We are going to have to stop going to you first in a minute. We are going to reverse this in a minute.

DR. SPILKER: You have asked three very different questions, all of which are very appropriate. In terms of local standards, the PRIMR group in Boston put on a two day program in October of 1998 in Arlington, Virginia, at which time they primarily were looking into generally the concept that I have described as central IRBs and I was interacting with Bob Levine of Yale in trying to get this done and Lou Lasagna and others.

And a lot of -- they had all the constituencies involved, all the different federal groups, all the different academic groups, associations and others. Many, many people came to that meeting --

there were about 75 -- with the belief at the start that the issue of local standards would be a huge issue and, therefore, they could not accept it.

One person, Dr. Friedman, from the Indian Health Service, was very clear on this by the end of the meeting and described the fact that all of his objections or potential objections were addressed.

I would say that everyone at the meeting -- or at least no one spoke out at the end, although they did in the beginning, that local standards were a major problem; that people in -- people say, yes, those -- you can have central IRBs but people in our area, we are different. We have our views. Which is not to say that there are not different views but even the Indian Health Service he felt could live with this and if there were specific cases or issues they could be addressed and that would -- might be -- so it might mean that in a certain number of -- with protocols or informed consents they would not accept the multi-center central IRB review but in most they would.

So I think that it is a very important issue, question, but that it really turns out to be much less of an issue or problem than one would anticipate.

The second thing you asked was about commercial IRBs.

Initially when they started about 20 years go, I, myself, was extraordinarily skeptical and not so much on the issue you mentioned of composition, which they meet all the national rules certainly and guidelines, but in terms of the ethical standards that they would apply, because I can think of -- as I am sure you can -- numerous reasons why one might wonder if their ethical standards were the same as the other IRBs that were not the professional ones.

Yet at this meeting of PRIMR at which not only western but other professionals were there, this question was brought up on the table. I certainly did not say a word but person after person attested to the fact that they knew of not one single case, not even an example, where one would question the ethics of professional IRBs.

Part of the evidence to support that is the fact that the U.S. Government has taken these professional IRBs into academic institutions to take over the IRB function when there have been problems in those academic institutions and this has happened not just once but in several cases. Not large numbers but we are talking about four, five or six. I do not know the exact number today.

But the point is I think, that that is

evidence in favor of the ethical standards and certainly their composition is correct. I do not know if like Yale where you need five -- Yale has 30 people on their IRB and then some of multiple ones, I do not know the exact numbers, although I think it is around 15.

Now the third question has to do with waiting for IRB reviews. I will not repeat the comments about the central IRBs. The most obvious one is for an IRB to meet more often. Now an IRB can meet more often in multiple ways and some of those can be determined by trying to think out of the box. For example, having certain -- if you -- you mentioned cases at your own institution. Perhaps if these are minor changes, they could then be approved by an expedited review by the chair or his or her designee.

And you are shaking your head yes indicating that that can be done.

There are ways in which local IRBs can say, well, how can we make this more efficient and I will stop there.

DR. SHAPIRO: Thank you very much.

Let me ask my colleagues, I have a long list now in front of me, to ask a single question and, if possible, address it to a particular person on the

panel but I think Dr. Welles has something you want to add on this issue.

DR. WELLES: I did want to add that, in terms of local standards, we do not find them so much an issue with regard to standards of practice. It is more that there is a great deal of variability as to what types of reviews happen in the IRB.

For example, we sometimes find out of the blue an IRB asking us about power calculations and study design issues and, quite frankly, often if they had read the protocol carefully, they would have learned that these things were in the protocol.

But I think implicit in doing large clinical trials is that there is uniformity, that you have to have sort of clean databases, that you have to have certain types of patients enrolled, and if an IRB were to sort of wish to enroll a different type of subject that would create a difficulty. Fortunately, that does not happen very often.

So with regard to commercial IRBs I think I had already mentioned that with regard to their concerns about safety we have never seen any qualitative difference between academic institutions and commercial IRBs.

We, in fact, audit all of our commercial IRBs

and we are not able to do that with academic IRBs. So we are very comfortable with the standards that are set in the commercial IRBs.

DR. SHAPIRO: Thank you.

David?

DR. COX: So this gets back to something that Steve Holtzman brought up, which I think was right on target, which deals with the scope in order to get people on board for more broad protections over all and not distinguishing, you know, what the money is.

And it also is a question in relationship to the FDA requirements now to -- in initial studies to stratify and then perhaps follow-up based on that stratification if you hit something.

And you will get the drift right away that it relates to how much you follow up individual patients as opposed to doing case control studies.

Historically, it seems like the pharmaceutical industry has really relied a lot on case control studies because they are cheaper than having to go back to individual patients but the more you do this stratification the more you are required to do stratification, the more you have to dig people up and go back to them and the more valuable each person becomes. Also, the more risk there is, in my

personal view, to the person.

So my question to you -- and I cannot actually, Harold, pick a specific person because I do not know who would be best in this.

DR. SHAPIRO: All right. I will pick in this group.

DR. COX: Is this just like smoking dope? I mean, this is not going to be a big problem or this is where life is going. I am very interested in terms of how the industry views this, because in terms of risks to people, I think it makes a big difference and the -- or -- so that is my question. Are we going to be really following people more and more and, if so, do you see that that makes the informed consent and the human subject's protections -- if it raises additional difficulties for you.

DR. SHAPIRO: You do not have to worry about the metaphor, just the question.

(Laughter.)

DR. WELLES: Well, I think, though -- I mean, typically we do -- by the time we get to Phase III -- very large placebo control trials and we do stratify often based on gender, race, you know, whatever -- age -- depending on sort of the issues within the trial.

And, yes, if we find some area where we would

like to probe more, we can use the data that we have already generated from within the trial to do that.

I think where we are concerned is that we will run into sort of gray areas or areas that may impinge on human subjects protection, is in the area that is -- we have not explored very much yet and that again is about collecting biological specimens, going back, trying to understand better, for example, why the drug worked in a particular group of individuals, why it did not work or why people had safety issues and that is where we find this whole area daunting, and are taking a very hard look at how to even get into this area given the logistical issues, the regulatory issues, and we are very concerned that it will become extremely cumbersome to have separate consent forms to reconsent individuals. We will not be able to find them, et cetera, et cetera. So there are a lot of issues that we are yet to -- that as a company we are looking at with regard to biological specimens but, you know, if we have generated data and it is all confidential we can go back and reanalyze and do subset analyses, and that is not an issue.

DR. COX: But, Dr. Welles, if I heard you correctly, you said that this is an issue at least when you have to collect materials that the industry does

not have or is working through right now and that you see it as a daunting problem.

DR. WELLES: Well, we as a company see that. I cannot really speak for other companies. I mean, as you are probably aware, the whole issue of pharmacogenomics has become of extreme interest and we would like to understand why our therapies work in people, why certain subsets of individuals do not respond, and hopefully tailor therapies for patients in the future, and we can only do that by collecting biological specimens and even -- you know, just the logistics of doing it is sort of daunting, and then when you add the whole layer of reconsenting patients perhaps and worrying about if you want to go back five years down the line and you have discovered a new gene and you want to look at whether that is up or down regulated in a tissue specimen, one could foresee that this would get to be a very difficult area.

DR. SHAPIRO: Thank you.

Yes, Steve?

MR. HOLTZMAN: Let me give -- I am going to go on that side of the table for a moment with our experience because Millennium has been one of the people in front on this. We have worked with about ten pharmaceutical companies, almost all of whom have

instituted the retention of samples now with the thought of doing look back pharmacogenomic analyses, and we have worked with most companies in terms of developing appropriate consent forms, so as to be able to do this.

This takes you into this whole area, which we kicked around for two years, about the notion of coded samples, the ability to continue to collect longitudinal information, and being able to go back and reanalyze a sample when, for example, it is determined that this single nucleotide polymorphism correlates with this drug response.

And so it has been a question, and I know Glaxo has been a leader in this area, and Bristol-Myers, with whom we work in the cancer area in terms of developing this, others have taken on this issue over the last several years, PhRMA formed a specific genomics kit and it was one of the -- that is a committee -- it is one of the key issues they are focused on of how do we structure these consents.

And I can tell you, from 1994, when we first started talking about his to where the practice is today, it is much more sophisticated having thought through this. This comes back, however, to some of the issues about what is human subjects research, how does

that get defined in terms of the medical records privacy issues, and whether you have structured it in such a manner where those studies effectively require reconsents and recontacts, which may not be preferable so it is a complex area for that reason but the industry has been all over it for the last six years.

DR. WANLESS: Could I just --

DR. SHAPIRO: Yes, please.

DR. WANLESS: I would like to concur exactly on that point. The issue might have been daunting at one time, but in terms of the oncopharmacogenomic collaboration that we have with Millennium, I think we have worked that out very well. The situation is more complicated, however, outside the United States.

DR. SHAPIRO: More complicated for what reason?

DR. WANLESS: Outside the United States.

DR. SHAPIRO: Yes, I know but could you explain why it is more --

DR. WANLESS: In terms of different legal approaches to this issue so we are not able to implement this in all countries.

DR. SHAPIRO: I see.

Yes, Dr. Spilker?

DR. SPILKER: The question regarded case

controlled studies, and I just wanted to comment that this means we are really talking primarily about Phase IV, drugs on the market, whether in post-marketing surveillance, large multi-purpose databases, or in terms of tissues and other biological samples archived in companies. In Phases II and III, prior to putting a drug on the market, there will be fairly few case control trials. Okay.

DR. SHAPIRO: Okay. Thank you.

Will, did you have a question before? I was not sure whether you wanted -- did you have a question? No. Will?

MR. OLDAKER: Yes.

DR. SHAPIRO: Please.

MR. OLDAKER: Any one of you, what is the current percentage of commercial IRBs as compared to institutional academic IRBs that you are using right now?

DR. SPILKER: There are said to be 5,200 IRBs in the United States, although that is a guess. NIH believes there are -- they have records of, I think, 3,600.

We have some people in the audience who can give perhaps more a up-to-date number but that was a number I heard in Congress. 1,600. At NIH they

are aware of an approximately 1,600 others they believe exist.

There are approximately 15 professional IRBs.

MR. OLDAKER: May I follow-up on that?

DR. SHAPIRO: Yes, go ahead, Will.

MR. OLDAKER: What is the percentage of professional IRBs that your company or the other companies would use in comparison to academic?

DR. SNIPES: Our utility of professional IRBs are still at a minimum compared to using local IRBs. Obviously, for some of the larger trials, which probably -- I do not have the exact number -- somewhere between 10 to 20 percent will probably use those. Eighty percent of the trials, though, when you are looking from, you know, Phase II to Phase IV, 80 percent of those will be using the local IRBs.

DR. SHAPIRO: Yes, Dr. Welles?

Dr. WELLES: This is just a rough guess on my part, but I would say as a company overall, we have probably used commercial IRBs ten percent of the time but as I alluded to before, I think we are much more interested in pursuing that -- their use more and more for the issue of centralization. It just makes it easier to start up studies.

DR. SHAPIRO: All right. David -- David, you already -- Bernie, you are next.

DR. LO: I wanted to change the topic of discussion to the issue of the informed consent process so not the informed consent form, which is so often the focus of interaction between investigators and IRBs but what happens with the potential subject and the investigators when they are talking about the trial.

I wanted to -- we have had a lot of testimony in the past here that it is very easy for patients who are eligible for enrollment in a trial to have a misconception that it is really therapy, as opposed to research, particularly when the person doing the enrollment is also a clinician who has responsibility for them.

I was wondering -- this is really directed to the three of you who are sort of on the front line so to speak -- to what extent do you get involved and sort of suggest to investigators how to handle that consent discussion in ways that first assesses whether patients truly understand what the trial is about and what they are likely to get from it and, secondly, in particular, in your work you have developed any sort of useful best practices that other investigators could use to sort of help dispel what has been called this therapeutic

misconception that what they are really signing up for is the latest and best clinical therapy, which it may well turn out to be but you do not know that until you have done the trial as opposed to doing, you know, a research endeavor.

So to the three of you.

DR. SHAPIRO: Dr. Wanless?

DR. WANLESS: Yes. I think this question is really more important, as you said, in a way than the actual approval of the consent form by the IRB. What we have done is to create a series of workshops for every clinical trial which we are undertaking and the consent form is, I would say, the most important part of that workshop and we deliberately role play how this consent form should be used and point out any particular issues that the investigators should really place emphasis on to make sure that the patient is truly making informed consent.

DR. LO: Do you have built into this process any assessment of the subject's understanding as opposed to what the investigator discloses?

DR. WANLESS: That is a good question. We have done that retrospectively in studies to find out that; yes, indeed. Again, I am sorry if -- I apologize if I keep bringing into this an international aspect

but consent form outside the U.S. is an even more, I would say, it is an area which we have had to pay even more attention to, because if the informed consent is written in the United States in U.S. language and then is translated, there are all the issues of whether this is really correct or not but actually that also applies in the U.S. if the person who is giving informed consent is not actually a native English speaker. Therefore, I think it is important to make provisions for translations of consent forms when necessary.

DR. SHAPIRO: Dr. Snipes?

DR. SNIPES: Yes. Along those same lines it is the language, the translation, even in North America, but more importantly the language can be right, but they still cannot understand it because it is written above -- it is supposedly an eighth grade level, but frequently I find we really need to be more at a third or fourth grade level in terms of really explaining to the patient what they are agreeing to and frequently we spend a lot of time. We will have a template of language. It is easier for the site to perhaps use some of the language they temporarily use because perhaps it is already in a written format or something of that nature.

And it is obvious if you read it and if you

had not gone to medical school or at least had not gone to high school, you would not understand what the risk might be, and so language becomes really important in informed consent to making sure that people can understand what they are consenting to.

And, also, one of the other areas that we have trained our company personnel when they are going out to sites, and we do have site initiation visits either as a group or individually, is making sure that standard of care, whatever that might be, is explicit in that document as well as the proposed treatment intervention because most of the time they are placebo trials anyway. And that we write out what we mean by standard of care, actually bringing everything to a certain level in terms of this, is the minimum kind of therapy you will receive, whether or not you have received the active treatment.

It is the informed consent frequently more than the protocol, that goes back and forth between sponsor and the IRB, and frequently it is just to make the language more simple.

DR. SHAPIRO: Could I just ask a question to either of you or Dr. Welles in this case? I understand the very careful procedures you are describing going through trials that you are conducting. In the

perspective you have spoken to, are those procedures any different if, for example, you contract the trials out for some independent firm to do them for you? Does that change in any way these kinds of concerns and focus?

DR. SNIPES: Again, when we are contracting out, we sit down with that contracting group and have these as minimal standards or expectations and sometimes, not consistently, we will say this is a part that we will still want to review all of these forms even though you are the intermediate for us at the site. And I would say 90 percent of the time we still review the template and informed consent.

DR. SHAPIRO: Thank you.

Dr. Welles?

DR. WANLESS: Could I just --

DR. WELLES: We --

DR. WANLESS: Oh, excuse me.

DR. SHAPIRO: Dr. Welles and then we will go to Dr. Wanless.

DR. WELLES: Yes. We, in fact, write our own template and we keep the language simple and, of course, that does get adapted and amended at individual sites and we are also -- we also have supplied translations when necessary, et cetera, and we do the

same in terms of -- when we have an investigator meeting we go over the issues but, quite frankly, we have not done a further assessment to see how it has been working. One can imagine again, when you have perhaps 100 sites, that you are dealing with different individuals, and it is very hard to do quality control in terms of what is happening when someone is in an office with a patient going over the consent form, and that is why I think our emphasis really is on making sure that the consent form is simple, clear, comprehensive in terms of outlining the risks and what is actually going on, and so we are sort of left with that, and we do review 100 percent of the forms even if we use the CRO.

DR. SHAPIRO: Dr. Wanless?

DR. WANLESS: I would just like to add, Dr. Shapiro, I think it is a very good question and in terms of choosing a CRO, we apply very stringent criteria, and if we think they are not complying with the correct way of obtaining consent form, then we do not use them.

DR. SHAPIRO: Thank you very much.

Yes, Dr. Spilker?

DR. SPILKER: Dr. Shapiro, I would like to comment on something else that Dr. Lo mentioned and

that was the possibility of quizzing patients about their understanding of the informed consent.

I think building into clinical trials assessing patients, and by a quiz, or however their understanding of this, not only can but definitely will have a very serious negative effect on all clinical research in the United States, whether it is academic, industrial or otherwise.

I think this is a very important point. This is not a positive approach. It is a very -- and I know he was not suggesting it but he was raising a question. This is a very theoretical comment that has been through the literature in numerous areas because of studies where patients have been grilled and quizzed.

I think the answer is present today and that is when patients are given a copy of their informed consent to take home they can refer to that at any time. They can share it with family members. They can show it to others and they can discuss it and digest it at their leisure.

When people are in the process of having the informed consent explained, they may not be in the best position to retain all the information, and just asking them the questions five minutes after that, which is

one approach, not the only one, I know, of assessing their retention of the information has not really been shown, I think, to facilitate things and I think it is a big threat.

DR. SHAPIRO: Bernie, is this a quick question?

DR. LO: It is a follow-up.

DR. SHAPIRO: Okay.

DR. LO: If I could just follow up because I think this is an important issue. In the recent gene therapy protocol at Penn, which has come under somewhat scrutiny, one of the allegations made is that the subject, Jesse Gelsinger, did not really understand that this was a Phase I study, and somehow was under the misconception that he might benefit, and was not really aware that there were serious risks.

So it is this -- you know, when something bad happens, in retrospect, there is the question raised of, did that person when giving consent really understand what was involved, and what was at stake, and so I pose that as an issue that comes up and I guess throw it back to the three of you.

Do you have any other suggestions of how -- and we would obviously all like to prevent those kinds of situations and the subsequent chilling effect that

that instance has had on further research. Do you have any other suggestions as to how to prevent those kinds of situations from developing?

DR. SHAPIRO: Dr. Snipes?

DR. SNIPES: Again my response is the same. It is still simplicity and clarity as much as possible because remember all -- not that particular situation but some consents are done in acute settings, and so this is the only time you have to take the snapshot in making a decision whether you are going to receive therapy or not, if you are having a heart attack or stroke or something of that nature.

The only way that seems to be closest to being honest and fair is simplicity of the language or having a third party come in outside of the clinician that may not be clinically based, but at least someone that can be a representative of that patient if, indeed, the language cannot get simplified enough and you think that the lay person cannot understand it. Then you have to have another lay person, who is trained, to help make that interpretation. Sometimes we cannot go from the clinical realm to the really basic realm of understanding what the risk/benefits are, but again it is simplicity in language.

DR. SHAPIRO: Okay. Eric, you are next.

DR. CASSELL: Well, I want to just follow-up on what that is and then a very short question. I mean, what you said, Dr. Spilker, about what it would do -- the chilling effect of questioning on consent, those are testable issues and I remember back in the early days of consent forms, when we were told nobody would be able to do any research if we insisted on this kind of consent and, of course, that is not what happened. And the next thing is, when people can take their consent form home, they can read it, they can discuss it with their family and bring it to church, or they can roll it up in a ball and throw it away, and they are not signing then. They are signing at the time they get it.

So those are issues that are testable, that could be discovered and they are very important issues, so I do not think we should dismiss it out of hand.

My quick question is in response to Steve querying about whether the embrace of the Common Rule would cause problems, you said, well, we would want to look at the language. Well, that is what it is all about. And so I am sure you have looked at the language or people have looked at the language and I wondered, if not now, but we might get the opinions about what part of the Common Rule's language would be

problematic for you or for your colleagues.

DR. SHAPIRO: Thank you.

Let's see. Alta, you are next.

PROF. CHARO: I wanted to just return us, if I may, to the question of the multi-center trials.

Dr. Spilker, forgive me if this was in the white paper which I read but can you remind me what the proposal was with regard to how the central IRB would be selected for any given trial? I understand it will vary from trial to trial but in any given trial how would the central IRB be identified and by whom?

DR. SPILKER: The NCI's pilot study is that they are setting up their own central IRB at NIH that would function in this way. The proposal that we are making -- I mean, that is fine with me -- the industry is saying that the sponsor of a trial, if it is an industry sponsored trial, that they would choose a group.

As a matter of fact, for example, the University of Texas has acted as a central IRB for a very large beta blocker study and we are just saying any IRB could be chosen to do that.

Now if this was -- for example, if this was a 50 site trial, and there are 50 academic institutions, and say the company -- the sponsor is not going to

pick, I do not think, a professional IRB, for example. I think they would pick one of those 50 that they felt was well respected and who would have the best opportunity of having its review accepted by the largest number of the local ones.

PROF. CHARO: But given your -- given the other comments about the way the market would work, with regard to centers that did not agree with some of the suggested issues -- you know, suggested resolutions of issues within the protocol, whether it is the kind of subject population, certain exclusions, compensation language, et cetera, this would certainly strengthen the market effect here in terms of excluding some centers from the ability to participate fully in the trial, wouldn't it? As opposed to a -- I do not know. I mean, any other -- a lottery system in which it was hard to know ahead of time what particular set of substantive rules would be applied.

DR. SPILKER: Those comments are pure speculation trying to -- and that was aimed obviously at the pharmaceutical companies and trying to suggest that the system might develop more strength at a later time. I think early on, if a number of trials -- centers wanted certain changes, the easiest thing for a company is to say, okay, you will have a separate

protocol depending upon power and other considerations as well.

I mean, I do not think one knows how this would exactly play out. That was only one scenario. I think we could write, you and I, ten others.

DR. WELLES: I would agree with that those are concerns are also quite speculative. Again, I would suggest that we have not had a lot of local issues that have come up that have caused us, for example, to rewrite a protocol or even have a substudy and that may be a function of the fact that when we draft a protocol, we disseminate it widely to experts in the field. We try to cover the broadest patient population possible, and hence, we have not had a lot of those kinds of difficulties.

DR. SHAPIRO: Will, do you have a comment on this particular issue?

MR. OLDAKER: No.

DR. SHAPIRO: Okay. You are on the list.

Jim?

MR. HOLTZMAN: Will you tell us who is on the list?

DR. SHAPIRO: It is Jim, Arturo, Tom, you, Diane, and then Will.

DR. CHILDRESS: Coming this late on the list,

obviously a lot of the points got raised, but as I would characterize your very helpful comments today in general terms, there is no need for fundamental changes in the system. We might need some streamlining here or there, perhaps in the direction of a central IRB, though following up on some previous comments we would have to really, I think, work through that to see whether there might be substantial gains in efficiency, particularly if local IRBs have a lot of discretion about consent forms. They cannot really work on the consent forms without reviewing the protocols, and that becomes, in effect, a pretty full review of what is involved but obviously we could pursue some of those directions.

But my main interest here is really -- and here is where Eric has already raised the question I wanted to raise, but I want to press it a little different way, and not simply ask for a later response to the question of whether there are problems in the Common Rule, but rather where have you hit problems.

Now the stored tissue sample area in terms of interpretation, may already be a problem, but could you just quickly identify three or four areas where you think there are problems?

I guess I was not sure in terms of Dr.

Spilker's comments about -- and others too about we would need to see the wording, whether that wording had to do with a government imposition of a requirement to follow the Common Rule versus language in the Common Rule itself, and so I would be helped a bit by a few comments along those lines.

DR. SHAPIRO: Anyone like to comment? Dr. Spilker?

DR. SPILKER: Very briefly, the Common Rule is not a problem for industry. I do not expect that there would be any problems if it was extended to every federal agency or every -- all amount of research.

I do not think that is an issue at all and so I am not anticipating that any language, although we can get back to it, is a problem on that but I cannot speak to -- for the industry on that.

I will tell you, though, where I do see the biggest threat, and again I emphasize the word is threat to research, and not just industrial sponsored research but all research, and that is in some of the privacy bills in particular that are in Congress today, which depending upon how they are implemented, could be very problematical and in addition, the HHS guidelines, and I was told that they had something like 35,000 replies to their 660 page -- some page, you know,

report from Dr. Shalala's office.

However, having said that, I think that those are the areas where, depending upon how HHS implements their rules, depending upon which bills are passed in Congress, it is sometimes the very fine tuning of those wordings which can have a very serious effect on research, and usually the research is not just that of sponsors but of academicians as well.

DR. SHAPIRO: Thank you. Any other comments along those lines?

Okay. Arturo?

DR. BRITO: When you all began at the very beginning, I was very impressed with the fact that your attempts or your efforts to adhere to the Common Rule, but you represent four companies, albeit very big companies, that have a lot of investments in human subject research. How representative are you of the industry as a whole? I guess my question is, what is the denominator here?

How many other companies are there out there, and are most industries having -- have relationships or interdependent relationships with academic centers such as yours seem to have for research trials, and are there other companies out there that maybe do not require the collaboration with the FDA or with academic

centers as yours do, so what is -- I just -- I am asking for a sense of -- I am trying to get a sense here of what is the adherence to the Common Rule by industry outside these big companies.

DR. SPILKER: This really is appropriate for me to answer. We are not from four companies. We are from three companies and PhRMA, which is the trade association representing the pharmaceutical industry's largest members and many of the smaller ones, as well as research affiliates, associates, et cetera, and foreign international groups.

Many of our members are multi-national, are either based in other countries, or have substantial operations worldwide. So PhRMA, where I am senior vice president for science and technology, I would say I am speaking on their behalf, not just because we have approached our members with a lot of these comments, with that white paper, which has gone through the entire industry, that white paper is an industry document.

Now you would also ask, well, continue the same line, a lot of the members of the biotech industry are not members of PhRMA, particularly the smaller ones. It is said that there are 1,200 small biotechs in America.

There are 800 plus members of BIO, which is a trade association, and someone in the audience is here representing BIO. I would say that the comments made really -- although I am not speaking on behalf of BIO, I cannot -- but I would say, in our experience, the comments made would include those of BIO.

There might be some very fine points of difference, but the biotech companies, no matter how small, have to follow the same rules and I would say the same considerations apply. When they do clinical trials, and a company might have three people and have one drug, the same rules apply. They are followed the same way. While they may be using CROs and contract groups to a larger extent, because they are forced to, they still are following everything identically so I would submit that what we are saying is representative of not only the large companies but the medium and small ones as well.

DR. SHAPIRO: Thank you. Tom?

DR. MURRAY: Thank you, Harold.

Thank you, panelists, for coming today.

You may be aware that the commission's previous reports have spawned at least a small industry of critics, that is everything we say tends to draw -- be read fairly carefully, by at least a few very bright

people, who try to pick at anything that might be moderately controversial.

And so I am going to ask you a question that I really want you to understand is not a hostile question, but it is a question to anticipate a kind of criticism that I can easily imagine being made of the report, this report.

In this -- in the capacity -- my capacity as a commissioner, but also in a role that I play as a member of a working group to the advisory committee to the director at NIH on gene therapy oversight, I have become aware of a few factors that suggest at least that, there may be conflicts -- potential conflicts of interest in research that the public is perhaps only dimly aware of but that would be sources of concern in some quarters, and I am going to mention two examples.

One is, since Bernie raised the Gelsinger case, my take on the Gelsinger case, at least what I understand of it, is not so much that Jesse and his father did not understand the form they were given, or the information, but they simply were not given all the relevant information about damage to primates and the similar trial about other side effects.

And the allegation has been made, or at least it has been suggested, that one of the reasons this

happened was because it was a small biotech company that really needed to have a successful experiment. So how does one guard against that kind of conflict of interest.

The other kind of potential conflict of interest, of which we have become aware, are organizations I can only describe as brokers. Groups of physicians forming themselves into coalitions, for profit coalitions, and then, you know, offering their services basically to obtain patients, to enroll their patients in clinical trials of various kinds. And then also -- there may be also at the other end, there may be fees paid to the physicians -- each -- the individual physician who enrolls each subject in the trial.

Now what I want to know from you, is what can you tell us, either today or where can we -- to whom can we write, or otherwise request information, about what the industry's positions are on these conflicts and how you formulate policies, if any, on such conflicts of interest?

DR. SHAPIRO: Dr. Spilker?

DR. SPILKER: I would like to take first the Gelsinger case, and you say what lessons can you learn from this. I think the answer in my perspective is

really at the IRB level. I do not think that your committee, in its report, is going to change attitudes and approaches of every physician in America doing clinical trials instantly, to achieve the perfect level that everyone here would like to have, but I think that you can reach every IRB in the United States, if you tell them, that they must ensure that the informed consent brings out the key points that they believe a patient must know.

For example, you could tell the IRBs, if you chose that any key points could be put in large type, could be put in bold print, in all caps, or anything else, to ensure that the information is not just conveyed verbally, but is seen by the patient and their family if relevant.

I mean, there are probably lots of other ways, but it seems to me that the focal point is, not the physician, and I do not know the Gelsinger case in detail by any means, and I am not purporting to know it, but I can understand -- I do know the issues and I think the focal point of addressing this is the IRB and their review of an informed consent.

And, if there are key phrases that they think should be in that informed consent, that can be not just put in there because if you are -- some of these

informed consents, let's face it, are ten pages or more. You are talking of single spaced material. You know, I do not know how much you start -- I mean, if the patient is going to read that but I do not even think all of us would read it, and you start going through and skimming things.

So I think bold print would stand out. That is the first point.

I do not know if you had another question but --

DR. MURRAY: Well, I really was not asking about how to --

DR. SPILKER: Oh.

DR. MURRAY: -- you know, how to set type on consent forms, Dr. Spilker. I was really asking how the industry apprehends these potential conflicts of interest, and how you deal with them, so that we can reassure the public that conflicts of interest are not affecting who is being enrolled in trials, and what happens to people in the course of trials.

DR. SHAPIRO: Dr. Wanless?

DR. WANLESS: I think your second question is a very appropriate one and one that can raise a lot of concern. Investigator's fees have been the subject of some concern recently, and I think that is an important

point. The fee that is paid to the investigator should be appropriate to what they do, but certainly not excessive.

And I will be honest for a moment, Bristol-Myers Squibb is a bit stingy actually, so we tend to give lower fees.

I do not think that -- the fee is certainly an element in that.

At the same time, I think the relationship that our monitors have with investigators is very important. If they -- if the monitor is -- can establish a very good relationship, and if there are issues of the type that you bring up, I think they will become aware of it.

And again that points to the need for us to train our monitors very carefully, and for them also not to be under the same kind of conflict of interest. In other words, not to show that they are able to induce their investigators to enroll large numbers of patients.

So I have not answered your question completely, except to say that I think you are right, and it is one that needs a lot of attention.

DR. SHAPIRO: Yes, Dr. Welles?

DR. SNIPES: I will reiterate --

DR. SHAPIRO: Dr. Welles and Dr. Snipes?

DR. WELLES: Well, with regard to the fees, and again I can only speak for Genentech, I cannot speak for the entire industry, perhaps we are just very conservative, but what we do is, we have a program, a software program, that enables us to look at costs of services rendered and when we formulate a budget, we just add up those costs and we allow for regional differences, and extra costs perhaps, for an academic institution because it is a teaching institution, and we try to fall at the 75th percentile.

So, perhaps, if that was applied across the board, it would actually be beneficial and it would certainly help us to compete. I mean, sometimes we find that investigators tell us that we are also tight, and it can be difficult for us to compete with regard to enrollment.

So -- but that -- so we are very strict about that. We just do not come up with a number and pay an investigator so I just want to share that with you.

With regard to the issue of conflict of interest and protecting subjects, I actually think this is very, very complex because, when an IRB looks at informed consent, they only see what is in the protocol. They see the background.

They may need to know what the preclinical data show, and the onus is upon us to share that information and we -- that is exactly why we draft our own templates, and we put that information in and how that is used at the site -- again it is very -- I mean, we do our best to educate people to try to control the situation, but again, when a patient is sitting in an office with a physician -- I cannot say what is being explained to that patient, and it is very difficult for us to control that. We just try to do our best, and we try to share all the information again in a very conservative fashion, because our interest is to protect patient safety.

DR. SHAPIRO: Let me -- before I turn to Dr. Snipes, who also wants to answer this question, I would say two things. One, given the fact that you both come from what you have described as especially stingy companies, we are especially grateful to have you here today.

(Laughter.)

DR. SHAPIRO: But in any case, my more serious question, and maybe Dr. Snipes will take it up in her own response, is there is this conflict on fees, but there is also conflict which is talked about with respect to something much more substantial than fees.

Equity ownerships and whatever it is that comes out of this, those kinds of issues that are much larger flows of money potentially, it may be zero I understand, so you might want to just in your response, Dr. Snipes, you may want to comment on that and the others may wish to after as well.

DR. SNIPES: Right. I guess I represent, I think, one of the third stingiest companies, too, when it comes to clinical development.

(Laughter.)

DR. SNIPES: I think it is --

(Laughter.)

DR. SNIPES: And I can only speak for my budgets, and my experience in cardiovascular, but again, the template is the same. You come up with a budget which you think is standard, and there are regional differences. It is more expensive to conduct a certain type of trial in New York City than it is in another part of the country, and we realize that, and try to allow for those differences.

But even within the company we have become more sensitized to incentives, and making sure that we are not giving incentives to merely get enhanced recruitment, and the original question dealt with the investigator coalitions and I think they are the

mainstay and there seem to be more and more of them every day.

One of the concerns that we have had, is really trying to make sure we still have a direct interface with the ultimate investigator who will be actually giving informed consent, and the intervention, because a lot of these serve as another interface.

So if you have a CRO and a coalition, it takes a long time to get to the person who is actually going to be giving the information, so we have tried very diligently at the end of the day, to work with these coalitions. But when we do site initiations and investigator meetings, we need direct access and training and education to the final staff that is really going to be training, and frequently, it is the physicians, but certainly the study coordinators and all that ancillary site personnel, that ultimately, is the one that patient has more interactions with as well.

Regarding the first part of the question in a generic sense, in informed consents, and I think there was, I know, very little about that case but you did mention that the information was not complete, perhaps some of the basic science data.

And I think we tell our investigators, that

the protocol does not necessarily include a lot of that basic science information, and that is why the CIB does go to the site. It goes to the investigator. The CIB being the clinical investigative brochure.

And in a Phase I study that brochure is basically, you know, the tox data, the preclinical pharmacology, and we really encourage people to read that information, because there may be excerpts that you want to pull out of that to actually put in your informed consent in the beginning, because the animal data is the only data that really you have to share with the patient.

However, you have to go back to my rule of simplicity. You have got to put that scientific information in a digestible fashion, and sometimes what happens is, it is easier to leave that out because, you will say, it will just confuse the patient.

I think our challenge as sponsors -- the challenge to investigators as well as to IRBs is to -- particularly in Phase I and early trials, is to get that necessary critical information up front in the informed consent in a digestible kind of language.

DR. SHAPIRO: Dr. Welles, do you want to add something?

DR. WELLES: Well, I wanted to comment on your

question about equity interest. I mean, most certainly we do not provide our investigators with equity interest in our company. I do not know whether that is the case with other companies. I cannot comment.

And now we are subject to new FDA guidelines, which when we file, we have to go around to our investigators and gather information, as to whether they are shareholders, how much -- you know, how much stock they own, whether their wives or family members own stock, and actually that is very cumbersome, but we do -- we are obliged to do it and we do it.

And we also now have to be very careful about people that we both use as consultants and investigators, and often it is a highly desirable thing to do, because these are our thought leaders and we want to sort of pick their brains and use their expertise and also get -- have them get experience with our drugs.

And so, we have to limit the amount that we can pay them over a given time period, and it is actually a fairly small amount so that creates some sticky issues for us as well.

DR. SHAPIRO: Yes, Dr. Spilker?

DR. SPILKER: I believe the answer to this issue of conflict of interest also lies within the IRBs

purview. IRBs today can, and many do, evaluate the financial arrangements of the clinical trial and that is up to them to decide as to whether or not they want to do that.

Some IRBs are also asking investigators to put in the informed consent the nature of the financial arrangement that they have with the company, and again, that is an IRB issue and I think that that is where it rightfully belongs, to be settled in terms of trying to achieve the right balance.

DR. SHAPIRO: Thank you.

Steve, do you have a question on this particular issue or a comment on this particular issue?

MR. HOLTZMAN: Yes, it is surrounding this. Okay. Trust me. A couple of requests for information.

One is, Bert, you mentioned some instances where the, I think, government asks for a commercial or what is called a professional IRB to come in and take over for an academic. If we could get documentation of that to the staff, I think that would be very useful. Is that possible?

DR. SPILKER: I think rather than coming from me it should come from OPRR.

MR. HOLTZMAN: Okay. That is good. So that

is one thing.

The second is, is Mike Warner still here from BIO?

DR. WARNER: Yes.

MR. HOLTZMAN: I wonder if we can, PhRMA and BIO, come up with an articulation of some of the concerns that are arising, for example, for the commission, in the context of the medical information privacy and these issues of what is human subjects research. I know we have written a bunch of stuff on it. If we could provide that, that would provide a context for the concerns.

DR. SPILKER: I think the way to address that is that we can give you, I hope, and I will check with our attorneys, a copy of our response to HHS, which was very detailed indeed.

MR. HOLTZMAN: So then the third is a challenge, I see, to us in industry, and I do not know what hat I am wearing at the moment, when you sit outside of an institution, as opposed to inside of an institution, it looks like this univocal big block so -- univocal, single entity -- so that if you are sitting outside of the academy, you say the university, the academy, but Harold Shapiro's world as the president of a university is very different than David as a chair of

a department is very different than Carol as a young, rising investigator. All right.

When I sit and listen to these questions about conflicts of interest and IRB shopping and whatnot, what I am struck by, is a failure for us, in industry, to give people a view into the complexity of our world.

I am a senior executive of a company, so I am responsible at the end of the day for the bottom line. Those M.D. s over there are the protectors of the patients, so when investigators in our shop, biologists want to push an experiment, their job is to say, wait, is it safe, do we have a moral right to do that in a patient. All right.

Somehow we need to let people see into this. The idea that we shop IRBs in order -- yes, patient accrual is an issue but this issue of -- that you were raising, Alta, if you write a protocol that most people are not going to accept, you are going to kill your patient accrual and you will never get your trial done. All right. So you cut your nose to spite your face.

The ideas of conflict of interest, all right, why is one concerned about conflict of interest? Because you are going to do a bad trial. You are going to get a bad medicine out there. I suggest you go look

at the list of companies in these big mergers, of who is the merger and who is the mergee. Okay. And see in which instances, it is the company whose drug for all the best will in the world, ended up having bad consequences out there in the marketplace, and is getting sued.

It is against our self interest to run bad trials that sneak through medicines that end up hurting people, and so that, even if you do not believe there is a moral reason to do it, there is a self interest economically, so how do we get this texture into the discourse is what I am -- really the challenge. All right.

Similarly, with these -- you know, the conflict of interest. There are 100 reasons going back to 19 -- what -- 88 when the rules came out, under Sullivan, that said clinicians should not get equity because of a conflict of interest. None of us give our clinical investigators equity for that reason.

Plus the facts that Bernice was talking to is that we have issues of insider trading with their relatives that we have to worry about, and plus new rules under accounting, in which we have to account for options differently with consultants.

So I do not know if it is a question so much,

as I sit having lived in these different worlds, and how do you give people an appreciation of the real texture of what is going on.

DR. SHAPIRO: Well, that is part of a rhetorical question, Steve.

(Laughter.)

DR. SHAPIRO: And perhaps you can help us get an answer to it but thank you very much. Those are important and relevant issues and it is a struggle always to understand --

DR. MIIKE: I think that was just one question.

DR. SHAPIRO: Yes.

(Laughter.)

DR. SHAPIRO: It is always hard to understand fully the complexity -- genuine complexity of any kind of organization, wherever it is situated in our society, so that is always a challenge before us, and we have to be therefore modest in what we think we believe we understand.

I have two more people on my list and then I want to change during the last 15 or 20 minutes of this. I want to change the focus to some of these questions but I want to first turn to Diane and then Will.

DR. SCOTT-JONES: I would like to hear one or more of you say a little bit about what you see as the major problems with the IRB system and the current system of oversight. As I have listened to you, it seems that you have said nothing terrible about IRBs so far, and some of the problems that you have raised seem relatively minor. For example, you talked about the problems with doing multi-site studies, and there perhaps being variability from site to site, but one of your specific examples from Dr. Welles was not that one site might reject the study, but that they might say you would need to do power calculations when you have already, in fact, reported that to them and that seems to be fairly minor in the scheme of things.

Yet when I read the report from PhRMA that is in our briefing book, it seemed very much more critical than your presentation to us has seemed so far. For example, the report questioned the training of IRB members. It raised the possibility of evaluating IRBs for their effectiveness. It pointed out that IRBs conduct minimal continuing review of ongoing research, which was a point made yesterday by Dr. Wax, an anthropologist, who spoke before us.

It seems to me from what I have heard so far, that the biggest problem that you have pointed out in

your dealings with IRBs, is that it may take a long time. It may take several months before you hear from them the outcome of their review.

So it seems to me, that you have not told us what the problems are, and that the problems in this report seem far more serious than what you have said so far.

Could you say what you see as major problems with IRBs and the way they function if you do see them as problematic?

DR. WELLES: I guess I would like to say in our day to day existence, the problems are mainly logistical. You have to -- from our -- when we wear our hats, we have large studies we need to get started, and we need to implement them in many institutions. So I think that is why that has been reflected in the testimony here today.

We are not watch dogs of IRBs so I think in some sense we have theoretical concerns. You know, what I -- I spoke to a number of colleagues to gather information before I came here, because we all have very different experiences, even within one company.

And what I have gleaned from all that conversation is that, yes, we do have theoretical concerns. One academic IRB does not equal another

academic IRB. What we hear is that, in some institutions, very junior people are put in, perhaps they do not have effective training. Likewise, if a commercial IRB -- perhaps they are very well trained. They are in the business of reviewing documents, and approving them, and they do it very efficiently. We can at least audit them. We do not audit every academic IRB so we do not really know what is going on within that IRB.

In terms of ongoing review, we do have concerns that perhaps safety issues are falling through the cracks, that they are overwhelmed with the number of safety reports, and often they are not disseminated properly or reviewed properly, but again, a lot of this is stuff that we do not get a hands on review of, so it is more of a theoretical concern.

DR. SNIPES: I agree with Dr. Welles and just to sum it all up for me is, that it would be very helpful if there was more standardization, and that is how we get to the default of commercial or central IRBs because there are a lot of inconsistencies, and where it focuses on me is, that if at times you do feel that perhaps the safety of subjects and patients are not optimal, because the IRBs are not looking at this data critically or in a timely fashion, and not at all times

do they all understand the guidelines, or implement the guidelines at the same level as other IRBs.

So some standardization or, as we talked about before, some accreditation or centralization of the IRB process would be very helpful to industry in knowing that when we go out and we are working with these IRBs that there is not always multiple learning curves that we have to go through for the various IRBs.

So the logistics day-to-day we have been alluding to, but there is an issue in terms of standardization, guidelines, and following implementing things appropriately.

DR. SPILKER: I would like to comment that again, the major problems are practical first, or the major problems that are practical, are two, delays and redundancy. We have addressed both of those. I will not repeat that.

The redundancy, though, would be addressed through central IRBs. That is redundancy among IRBs of having 200 sites have IRBs when there is really no need for that. And that is universally agreed to, that is not just an industry perspective.

Secondly, you talked about the white paper we prepared. We were mainly trying to bring up some of the topics in the HHS IG, inspector general report.

When they talked about training -- keeping in mind that we do not interact directly with most IRBs, but through the investigator, we were saying training is something that makes good sense. It could be that handbooks would be prepared, because most people go on to an IRB as a volunteer, and it is getting harder and harder for institutions to find those volunteers. They do not know what is expected of them, and it is really in some cases, at least, a lot of on-the-job training.

And we believe that, why shouldn't you have a little bit more standardization in so far as having brochures or handbooks prepared, that could be given to them and so we are going along with that.

I do not believe that we are pointing out serious errors. We think the system is working well.

I would remind you that the first title of the inspector general's report which was "A System in Jeopardy" was changed to "A Time for Change" because of a lot of people's complaints that they were really overstating the issues, and had only surveyed very few IRBs. I think it was eight or so. And also the people doing this were not really doing the work for GAO -- not GAO, sorry, inspector general -- were really not that knowledgeable about the details.

One of the issues is that, over the years,

many people have put up proposals giving -- proposing to give the IRBs more and more functions to do. For example, one was they should be the group to approve of INDs, to put a drug into humans for the first time. Now -- and the point is, many people today believe they are monitoring clinical trials, which they are not.

And so there is a lot of mythology, a lot of belief that they can be doing a lot more functions, they are an easy target group, whereas these are overworked people who are just trying to keep their heads above water, on a voluntary basis and institutions are having a tough time.

We are looking for ways to make their life easier and yet keep it effective.

DR. SHAPIRO: Thank you.

Will, you had a question?

MR. OLDAKER: Dr. Snipes, you indicated that -- I think in your original presentation -- that the time efficiencies of the IRBs was a problem and time is money and if you had to wait eight weeks or 16 weeks, that can slow down projects, and if you had to go back, it could be, you know, 16 or 32 weeks, that becomes an enormous amount of time. That is half a year.

Do you find that the commercial IRBs or their equivalents are faster and more responsive?

DR. SNIPES: Generally, in a sense because they read the protocol well, they know the CIB, they may have actually had experience in this particular therapeutic area, so they can anticipate, or know where to find the answers to questions fairly readily, and also, it is just an efficiency because they are going to be seeing -- covering 50 sites versus, you know, 50 independent IRBs.

So the efficiency is definitely there as well as the quality that we are getting out of them.

DR. SPILKER: And they meet every day.

MR. OLDAKER: And a second question to you. You talked, at least in some of the written materials that I read, both about best efforts or good practices, one or the other, good practices or best practices, and a certification process. And, secondly, you talked about centralizing. Both things, it seems to me, would go to the efficiency of the process.

If there were a regulatory apparatus set up, that basically also set up standards for certification, although it be industry certification, and that there was a methodology for centralization, set up with some protection so that form shopping would not occur, would you think that that would increase the efficiency of the process in a helpful manner?

DR. SPILKER: Absolutely with one quite different -- important caveat to what you said. Industry is absolutely not proposing -- not proposing that we accredit IRBs. This would be done by either the government, and there are a couple of -- and certainly a couple of government appropriate groups are looking into it, primarily OPRR is looking into it. There are some academic site groups, associations looking into this that -- and also PRIMR is looking into this, and there may be other groups as well but I know of several.

We think that, as long as the group that does this is independent and responsive to the various stakeholders, that that is fine. Industry does not see itself as a group that could, or should be doing this, but would like to be involved with those groups to at least provide input.

DR. SHAPIRO: Yes, Dr. Welles?

DR. WELLES: I just want to concur with Dr. Spilker. I think centralization would be enormously helpful for us and we certainly would want groups, that would be external to us, that would have some kind of certification process that would be ongoing.

But back to the original question I just wanted to add that the situation is tough logistically

for us. It is livable, but not optimal but we certainly would not want to see an expansion of IRB responsibilities, and again, a lot of this is -- these are things that I have heard, you know, perhaps IRBs would be reviewing the adequacy of the study and whether we should even be doing these kinds of studies.

And, you know, as industry, we certainly would not be doing studies if there was not an unmet medical need in that area.

To speak to Steve's point, I think we are our own toughest watch dog in a sense and I would like to convey that to you as well that we have very strict internal controls. We have very serious peer review of our clinical programs that we hold safety up as sort of the highest concern. We have our own safety review committee. We have -- if a safety issue comes up we convene an internal safety committee and typically with our larger trials and sometimes even in Phase II we call in an external safety board so we are our own watch dogs as well.

DR. SHAPIRO: Thank you very much.

Bette?

MS. KRAMER: Yes. I have a couple of concerns and they are captured in the comments that Steve made a short time ago but I would like to be more specific.

My concerns go to the practices of smaller companies. You all, the three of you are sitting here representing very large, well established companies that have a lot of resources, and I think your comment that you are your own internal watch dogs is right to the point -- my point.

I am more concerned about smaller companies, perhaps even some of the start up companies with less resources, that cannot employ their own internal watch dogs, that do not have all of their own internal systems of controls, such as you have described that you have today. Perhaps in many cases they even have a whole lot less to lose.

I am concerned about the practices of these companies, and my other concern is -- and this is a point of information question -- to what extent are community hospitals used in these trials and the smaller investigators that are typically associated with community hospitals as opposed to academic institutions?

And can you give us some insight as to how we can know what the problems are in this particular sphere?

DR. SHAPIRO: Yes, Dr. Wanless?

DR. WANLESS: I am not going to answer the

first question because I do not know.

To the second question, did you mean it with regard to community hospitals, how the IRBs are functioning?

MS. KRAMER: No. I meant it even more generally than that. Not just how their IRBs are functioning because I know it is with difficulty, but to what extent are smaller -- are community hospitals used in these large clinical trials? Perhaps they are not used at all. As I say, it is a point of information. I do not know.

DR. WANLESS: Oh, they are certainly used.

MS. KRAMER: All right. Well, then if they are used, do you have different problems with regard to their IRBs because I know they have far less resources than those in the academic institutions? So could you perhaps broaden some of the remarks that you made earlier with regard to this particular sphere?

DR. WANLESS: Well, I think again the problems are logistic ones. They probably do not meet as often as we would expect in an academic institution, but I think these are problems that we get around, and the type of research done in these hospitals is excellent quality.

DR. SPILKER: I would like to second that and

say that, basically from your consideration, I think the problems are identical. The issues are identical. They may have fewer trials but then they are going to have fewer efforts expended on this and it may be harder for them to get volunteers. But there may be some differences from hospital to hospital but if you take the entire group compared to the academic institutions I do not think you will find differences.

And I would like to ask you a question. When you say -- to clarify. When you said you are concerned about small companies, and that was a quote, what are your concerns specifically, and then we could address that part of your question.

MS. KRAMER: Well, I think there are two general concerns. One, that the companies by virtue of their lesser resources, both financial resources and personnel resources, are not in the same position as the three companies that are represented at the table this morning to set up their own internal controls, to draft their consent forms, to have their own internal monitors.

I mean, I am just touching on some of the areas that you said that you do in order to protect the human subjects with whom you are -- who are participating in your trial so that they do not have

the personnel or financial resources to do that.

And they have -- I do not mean to sound paranoid, but they have a whole lot less to lose than the companies that are sitting here at the table here this morning.

DR. SPILKER: Thank you for clarifying that. I would like to make one important point and that is that IRBs do not have different standards for trials submitted to them for approval by large companies or small companies and I think that if that were part of your report that would be something that would not -- I do not think any small company would blink at personally if you had that as a principle because I was head of a very, very small company.

We did many clinical trials on a lot of drugs and they were very small drugs. We certainly treated our products, even though they were tiny, with the same care the big companies do but with fewer resources and we expected IRBs to look at our trials the same way they did at those of my colleagues here this morning.

MS. KRAMER: Can I just ask a follow-up?

DR. SHAPIRO: Yes. And then we are going to switch topics.

MS. KRAMER: My concern is not that the IRBs would treat them differently. What I am saying is a

lot of the comfort that I personally am taking from this morning's exchange is that in terms of the companies that are represented at the table, before it ever gets to the IRB they have within their own structure a lot of safeguards that a smaller company might just not have the resources to provide. That is -- I am not --

DR. SPILKER: Okay. I understood that point but what my answer -- I should have clarified it a bit more -- is that I think you are saying how can I take comfort. I am saying while I am not suggesting the small companies who do not have those resources, I agree, are going to behave differently.

I am saying you do have the comfort of knowing there is a fail safe mechanism. That fail safe mechanism is the IRBs that are going to ensure everyone in this room and all of America that small company clinical protocols are the same. I am not -- I could not address possibly any other issues prior to that, but I am saying even if there were an issue it would be controlled at the IRB stage.

DR. SHAPIRO: Dr. Welles?

DR. WELLES: We do forget here that we have another fail safe and that is the FDA, and a drug will not get into the clinics unless the FDA has approved

the IND, which presumably has all the preclinical data, the manufacturing data, the protocol itself, and those of us in industry know that we have very extensive conversations with the FDA before we can get that protocol out to the clinics, and to our investigators, and they may raise safety concerns and ask us to lower doses, add doses, add subjects, whatever it is so that is an additional safeguard before anyone can even get into the clinics.

DR. SHAPIRO: I would like to just shift the focus of our questions here for the few moments we have left. We do not have a lot of time left this morning. I am already very grateful for the amount of time you have spent here with us.

And that concerns another study we have underway in which some of you may have some observations and that is one of our studies has to do with international research, by which we mean research sponsored by U.S. Government and U.S. companies but carried out abroad in consultation with others or in collaboration with others, perhaps, or in collaboration with your own units that might exist abroad.

And one of the things that at least I am interested in is any general comments you might have about what are the motives that cause you to want to

study something abroad? I mean, I can imagine many legitimate motives for doing it. One is that, you know, the populations you need to study are there and so you have to go there in order to study the problem obviously.

Another is that it might be more effective and efficient to do it there for various legitimate reasons, et cetera. I can imagine a lot of quite legitimate and important, and compelling reasons indeed to do this abroad.

But I am wondering if -- I do not know, Dr. Wanless, I should address this question to you first but I really address it to anybody there. If you could just give me some insight into that and I am really talking at a rather general level here, I understand, and responses at that level would be very much appreciated.

DR. WANLESS: I think there are, indeed, some obvious reasons why we do this. Bristol-Myers Squibb does, in fact, have research facilities throughout the world and that includes now not only Western Europe but Eastern Europe and what we call "the rest of the world," which is the part that I am responsible for.

(Laughter.)

DR. WANLESS: So that is --

DR. SHAPIRO: It is the biggest part.

DR. WANLESS: So that means Latin America, Africa, Asia, Australia.

Firstly, there are indeed certain diseases which are more prevalent in those areas. We are currently carrying out a large program in hepatitis B and, of course, the largest numbers of patients with hepatitis B are in Asia.

Secondly, the reality is if you do not do clinical studies in countries you will not have a market there either, so they are the first part in creating the market for the drugs in the future.

In terms of efficiency it is true that we are able to develop worldwide programs that reach the endpoint faster than if we were to do everything in the United States, or in Western Europe, for that matter.

What I would like to add, though, however, and this is, I think, perhaps the points that might be more interesting or more relevant to you, especially in the developing world, I think all of the ethical issues that we have been talking about, the IRBs, the need for informed consent, these are magnified enormously and I have become very much aware that during my time looking after "the rest of world," as I said, and they cause me a lot of personal concern.

And, therefore, we deliberately spend a great deal of time making sure that our investigators fully understand what the informed consent process is and a bit beyond that because if you imagine, for a moment, in developing countries it is very likely that some patients will not have access to this therapy by any other means than if they go into a clinical trial.

And that is -- could be seen as coercion and we have to be very careful to make sure that the patient really understands what this is all about.

So just to say there are lots of reasons to go to these countries, but I do not think that they should be done lightly and I think it is imperative that if we are concerned about the welfare of patients in the United States we must also be equally concerned about those that go into our trials in the rest of the world.

In that regard we do not conduct trials outside the United States exclusively, so our trials are multi-national and will include centers in the U.S. as in Southeast Asia or Latin America.

DR. SHAPIRO: Can I just ask one question which is a little more concerned with the detail and you may have thought about this or may have something to say about it?

When you take issues of informed consent, which you have already mentioned in terms of translation of documents, it is difficult to get the language right and so on and so forth, those are challenges themselves, but if you think of two aspects of informed consent, one is, you know, formal, you have to sign this paper which has some language on it, and the other is a kind of focus on the quality of the informed consent process, the substance as opposed to the actual form that you use.

In your experience where do you focus your efforts here? Do you still try to get the same kind of paper signed so to speak or do you feel it is appropriate that really what you focus on is the substance of the idea here and try to deliver that in the most effective way given the different environments you find yourself in?

DR. WANLESS: Yes, it is the manner in which informed consent is obtained, the actual process that we should pay attention to, and again the type of workshops that I mentioned before, we are extending throughout the rest of the world.

DR. SHAPIRO: Thank you.

Dr. Snipes, did you want to say something?

DR. SNIPES: To answer the latter part of your

question, yes, content really drives it because there are so many -- or uniqueness in terms of cultural differences. We have to take those things into consideration. There are local companies in each of the territories and we actually use them as a guide in terms of what is the most appropriate manner or forum or language to get the content. The content being the same, but the process of doing it can vary greatly.

To go back to the first part of the question in terms of international research again, obviously it is in part disease driven but, you know, I come from a U.K. based company, Glaxo Wellcome, so actually the U.S. is a local operating company in a sense and so when we look at developing or starting studies and protocols, really the world is the map and you sort of go from there and then start looking at whether or not they have the resources and the efficiencies to do the study, but actually the world is our original map in terms of setting up trials, not just the U.S.

A lot of these trials, I should say, do fall under -- they will support our NDA with FDA and we realize that we have to go through -- have the same kinds of standards that we would have for a U.S. based trial because those subjects -- those trials are subject to FDA audits, the same types of implications

fall on those sites and we will be at risk of not having that data being analyzed in the NDA so we really have to make sure that they meet the -- at least the minimum standards that are set forth in the U.S.

DR. SHAPIRO: Okay.

Yes, Dr. Spilker?

DR. SPILKER: Many of our companies are multi-national, and if a clinical trial conducted outside United States is going to be used for a U.S. submission, the FDA has very, very strict rules on IRBs, or ethics committees as they are called outside the U.S., and informed consents, and these standards must be adhered to by all companies conducting international trials if they expect any of those data to be used in the United States.

I would like to comment also on the last question before we were on this which I think is critically important for your company -- I am sorry, for your group in terms of thinking about these fail safe mechanisms, and that is that -- and I really want to thank Dr. Welles for reminding me of this -- that not only does the FDA look at the protocols when a drug is going into humans, they look at every clinical protocol that is conducted. It must be submitted to FDA. But in addition, if NIH is paying for any of

this, they will probably get copies, but often there is a department regulation in your institutions that the department has to receive a copy and look things over. If the work is being done in a clinical research unit, they will often, and sometimes, have their own groups to even approve the protocol as well, as well as even company consultants.

And while small companies would not have the resources to do the activities that you described for sure, in some cases at least they will be bringing in consultants to advise them on the protocol and that would include consideration of some of these issues, and this is not even to mention the IRBs.

My point is IRBs are far from being the only fail safe, that there are many parts of the system that are operating today and function in that way.

I do have one final comment on the international one and Dr. Meslin has been very acidulous in following up with PhRMA on an international questionnaire. I wanted to make just one comment on it.

This questionnaire was designed for individual researchers. Fine. It was not deemed appropriate by the companies that we share this with, which was a large number of companies, to be addressed. It was not

an easy questionnaire to just retail or rework for individual companies.

We were not being difficult. We were not trying to be difficult. We were trying to be cooperative but when you had a questionnaire that was designed in one way and being addressed in another, it created problems and we felt we could not complete it.

DR. SHAPIRO: Thank you and I very much appreciate that, and we will certainly continue to work with you. We had not meant to impose upon you something that was inappropriate and so we can carry those discussions on in some appropriate dimension here.

Well, first of all, let me begin by thanking you all. We have kept you here for over two hours, almost two-and-a-half hours. I really very much appreciate your coming today and your very thoughtful responses to our questions.

I certainly welcome any further observations any of you might have regarding these topics that you think might be of assistance to us. We would certainly be glad to consider them. Any input that you could give us would be very valuable to us, indeed.

I will tell commissioners we will follow-up on a number of the questions that you raised today, which

looked for information and so on. We will certainly follow that up. And as we go ahead, we will certainly share with you any materials we produce. We produce drafts of all of our reports before we move to any final resolution.

We will take the liberty of sending them to you. You are not required to do anything with them. You are busy people, but any feedback we get from you, of course, would be extremely helpful to us because we are interested in making as thoughtful a report as we can and your perspectives, indeed, are very helpful so thank you very, very much for coming here today.

We will take a 15-minute break now and reassemble at quarter to 11:00.

(Whereupon, at 10:30 a.m., a break was taken.)

PANEL II: PRIVATE SECTOR ROUNDTABLE

RESEARCH FIRMS

DR. SHAPIRO: Colleagues, I would like to get together, please. Our guests are waiting for us and we ought to proceed.

Thank you very much. Once again let me, first of all, begin by welcoming our panel. Thank you all very much for being here today.

Some of you may have been here during the previous panel here and may have heard some of the

issues that were on our minds. We have with us today some representatives of companies which in some sense are quite different from those we heard from just a few moments ago. They are what we call the biotech companies as opposed to the pharmaceutical companies but that is just a convenient way to refer to it.

We are really very grateful that you have taken your time to be here today.

As you know, I will just repeat what I said at the beginning of the previous panel, that our primary interest today really focuses on our project, which is what we call our oversight project, which is trying to assess whether the current federal system for the oversight of human subject protections is really adequate and if it requires any change in any way given now that it is some decades old and time and circumstances change a great deal in that period or whether basically it is serving us quite well and whatever changes it might need might just be on the margin.

Now I know you are not -- I do not want to use the firm biotech firms. These are research firms that are really here and carry on a much broader set of issues and concern themselves with a broader set of issues.

So that is really our main interest and maybe I could start off just by asking a question and the rules here is you just press on this, the light goes on, and I try to recognize whosever light I see first, and leave it on while you are speaking because that is what amplifies this through the room.

We began our -- one of the concerns we have had really from the very beginning of our commission was whether the federal protections, which really are protections of independent review and informed consent, basically the two foundations on which human protections of human subjects are constructed, really extended far enough. That is, as you know, we get into that scheme when you have experiments that use human subjects if either they are sponsored by the federal government or they somehow come under the FDA auspices, but we are really -- one of the things I am particularly interested in is whether that needs to be broadened to include, for example, all privately funded research or any research anywhere regardless of its funding that uses human subjects.

So maybe I could start off that way by asking what your views on that particular matter are. I do not know which one of you wants to speak first.

MR. McKENNA: I would be happy to do that.

DR. SHAPIRO: Press your button, Dr. McKenna.

MR. McKENNA: Okay. I will raise one point about that in that -- well, first of all, maybe I -- what I would like to do is to start by just giving you a little bit of a background because --

DR. SHAPIRO: That is fine.

MR. McKENNA: -- we are not biotech firms.

DR. SHAPIRO: Right. And I apologize for that.

MR. McKENNA: And to some extent the -- it is a little bit hard to use the word "research" and say, well, what is it that these people do so let me say a little bit about that.

DR. SHAPIRO: Thank you.

MR. McKENNA: We are an organization that does contracts and grants with industry, government, academic institutions and foundations. Some of the work is investigator initiated, some is collaborative, as a partner with other investigators. Much of it is serving as a support contractor to government agencies in support of their research initiatives and where the work in which the contractor organization is doing may be considered research or may not be considered research but is simply operational support and the responsibility for the research lies with others.

I think that the problems with human subjects issues that we see actually varies a bit or maybe I should say quite a bit depending on the type of arrangement that we -- you know, that is employed in the contract. So the devil is in the details.

With the investigator initiated research, I think that I have only been here for part of the session but I would say for my part we do not have much to contribute that is any different or more than what you have heard otherwise.

On the -- I want to come back to this point of these differences in a bit and talk about a special problem that we have but, first, I guess, let me say that as an organization that is a multiple project assurance holder the notion that there are different standards for -- depending on whether a contract may have human subjects requirements in the contract is not right because at least in our case the most recent multiple project assurance that we reached with OPRR requires us to apply the same standards to government and industry work alike.

DR. SHAPIRO: Is that -- and that is the same thing that is true of many academic centers which have multiple product assurances. Is that common in the industry as you understand it that most places either

through multiple project assurances or through any other set of commitments they may have treat their human subjects or have whatever protections are appropriate for human subjects pretty much the same regardless of the source of funding? Is that common to all your -- yes, Dr. Ross?

MR. ROSS: I would say, for us, no. Most of our work -- we do not do clinical work and we are definitely not a biotech firm. I would classify our work as demographic survey research, evaluation research. We have a multi-project assurance through USAID. We have -- we use single project assurances with the rest of the world.

Clearly with the USAID work the standards that are being maintained are quite different. We did not even begin to consider the USAID projects until about three years ago when USAID adopted a very different stance on international work and said we really need to start looking at these.

The difficulty with much of the international work is our collaborators are usually the statistics agency in that country. Generally the statistics agencies in those countries do not view the participation in the research as voluntary. They view it as mandated, much as we view, let's say,

participation in the census. It is mandated that those who are selected participate.

In addition, given cultural differences, what we are told is if you tell people this is voluntary, that you can withdraw at any time if you change your mind, and if we present that the way we typically would in the U.S., we will create a demand characteristic that will cause people to think, oh, I am not supposed to do this. That is just an example.

When we confront situations with DOD funded research we find something else entirely. I would say we were -- we really did not know how to handle that when we were assuming that we could offer the same kind of confidentially or anonymity we would be accustomed to in non -- in civilian – research, but we were told instead that, one, we could not promise confidentiality and, two, we could not promise that there would be no ramifications based on responses on the assumption that the respondent's body was a weapon and if anyone was doing anything inappropriate with that weapon that that was considered a violation of their obligations to their employer.

So we find very, very different standards based on the situation and it is not something that we really know how to deal with. We accept the fact that

there are differences.

DR. SHAPIRO: Thank you. Any other comments on this question from the other panelists? Yes?

MS. COLETTI: I think our experience is more similar to Mr. McKenna's where our corporation does a variety of work similar to what he has described. The largest share of our work is done for either federally or state funded governments. We also do some work with foundations and other public sector or nonprofit funding organizations.

Another smaller portion of our work is in doing business with private sector clients and that includes some pharmaceutical companies. What we have chosen to do as a policy in the company is that all of our work that is in these -- what we call our government sector -- is all subject to potential review by our IRB and it is regardless of whether it is funded by a federal government, a state government, an organization, a nonprofit or foundation.

It has been in the last few years that we have gotten into business related strictly to clinical trials of investigational agents and because the history of our company has been doing more social and policy research, and that is the strong expertise of our IRB, we have elected to coordinate and work when

necessary with other commercial IRBs or other collaborative IRBs to assist and do the IRB review of our clinical trials work because we felt that needed additional expertise that our IRB built on our foundation of social and policy research could not really address all of the clinical trials issues.

So we sort of have that two pronged approach but in principle -- I mean, our policy is to apply the same standards to all projects throughout the company.

DR. SHAPIRO: So if I understand the case at Abt that all the work involving human subjects would have IRB review somewhere. It may be your own. It may be someone else's where the expertise is sitting -- at least more expertise than you believe you have, but all the work would be IRB reviewed one way or another.

MS. COLETTI: Yes. As long -- I mean, that is -- all of it would be subject to potential IRB review. We have a lot of projects which we might talk about a little bit later today where you get into a gray area where it is not always clear that IRB review is required. It may be exempted from IRB review by the regulations but the IRBs purview is to look at everything equally across the board regardless of funding source.

DR. SHAPIRO: I apologize. I misspoke. I did

not mean to say it actually had to come before the IRB because it might be exempted or expedited and so on according to existing regulations.

MS. COLETTI: Right.

DR. SHAPIRO: Yes, Dr. Kaul?

DR. KAUL: I would just like to add to what Anne was saying. I think we have chosen this bipronged approach because when we do clinical trials we are operating under FDA regulations, which are different --

DR. SHAPIRO: Right. Required.

DR. KAUL: So I just wanted to sort of throw that in.

MR. McKENNA: Could I add something, though, to finish off the answer to your question?

DR. SHAPIRO: Oh, certainly. Yes, absolutely.

MR. McKENNA: I think that it sounds like you have three organizations here that all have multiple project assurances.

DR. SHAPIRO: Yes.

MR. McKENNA: There are many smaller organizations who do not and so what we may say about the extent of our reviews clearly do not apply to organizations who do not have an MPA and, therefore, are not compelled to review, you know, the broad scope of things and may review only what appears to be

required to be reviewed under the specific contract in question.

I guess the other thing I wanted to say is that the group that you have here are all organizations that are large in the social and demographic research area. They are major government contractors. They all do some private industry work but we do not represent the bulk of the CRO industry obviously.

DR. SHAPIRO: Yes. I understand that. Thank you very much for the clarification.

Larry?

DR. MIIKE: I just wanted some clarification, for example, from Abt. You obviously do directly research in the socioeconomic area but when you get into the clinical trials area you are basically like Mr. McKenna then. You are contracting with a pharmaceutical firm, you are managing the complexities of multi-center trials, et cetera.

In your case, Mr. Ross, you are distinguishing about what are your obligations domestically versus internationally. Is that what I hear you saying?

MR. ROSS: Bear in mind the kind of research we do. We do not do anything vaguely resembling clinical trials.

DR. MIIKE: Right. And when you talked about

the kinds of research that you assist other countries in doing you are dealing with mainly statistical agencies. Are they typically government agencies that you are dealing with?

MR. ROSS: Typically, we are always working with a government agency. We may also be working with universities. On rare occasions we are working with private organizations, but that is very rare. There is always a government agency involved.

DR. MIIKE: Okay. And do you perceive that when you work with the government agencies abroad that were you working with them in the United States that you would have had to change your procedures in terms of human subjects protections or would those activities since they are probably minimal risk -- well, except that the way you describe it some of these are not minimal risk but would they have, in general, fallen under the exemption categories under the current federal regs?

MR. ROSS: Yes.

DR. MIIKE: Because many of the kinds of activities with government agencies are.

MR. ROSS: Yes. Most of them would fall under -- could fall under the exemptions. We would look at them because if children are involved we would take a

look at the projects anyway because they are vulnerable populations. However, the most clinical thing we do is an occasional seroprevalence study or, let's say, a study of anemia among young children and women of child bearing age. That is as clinical as we get.

DR. SHAPIRO: Thank you very much.

Let me ask -- I am sorry, Alta. Did you have a question?

PROF. CHARO: No.

DR. SHAPIRO: Let me ask a question. All right, Rhetaugh. I do not like to ask all the questions so, Rhetaugh, you have a question, go ahead.

DR. DUMAS: Well, I needed some clarification. I noticed that both Mr. McKenna and Mr. Ross are IRB chairs and I do not have a vitae of Mr. Ross but, Mr. McKenna, can you tell me a little bit about the argument -- your organization that has the executive vice president and chair of the company serve also as the IRB chairperson who also participates in the project -- in the development of technical aspects and review of projects internally? How do you juggle all of those multiple responsibilities and assure that there is an objective review?

MR. McKENNA: Well, I think there is -- first of all, if it says that I am in detail -- you know,

involved in all the details of the project, generally that is far from true. I am quite a ways from the details of the project. If I am very close to the project I cannot sit on the -- as either the chair or even a member in reviewing an individual project.

I think that there is a -- you know, there is always a tension between these roles and one has to, you know, do the best you can at being careful to be sure that you are, you know, meeting the -- meeting the standards that one would expect of an IRB member, and I think I am able to do that.

I think I have a good understanding of the organization and I am able to make sure that people understand the requirements and that I think it cuts both ways as both a positive a negative.

DR. DUMAS: Was it a deliberative decision that the executive vice president and chairman of the company would also serve as the IRB or did that just happen?

MR. McKENNA: It is a historical thing. I was actually -- I was in -- I have been in the -- I have been with the IRB for probably close to 15 -- 10 -- over 10 years anyway and I have only been in this position for about six.

DR. DUMAS: Oh, I see.

DR. SHAPIRO: Okay. I have some questions.

Larry, do you have a question?

DR. MIIKE: Yesterday we heard from people who did demographic research, historical research as well as science research, and several of them were quite adamant about how inapplicable the Common Rule is. Now you people do both so can you -- I would like to hear from you who do both whether they are just fundamental differences and you would rather dump it or change it for one side or it works fairly well?

MS. COLETTI: I do not think that there is a completely straightforward answer to that question because there is such a range of some of the -- what we call our social and economic policy research. There is such a range involved there. This is actually one of the things that we talked about a lot in preparing to come to this meeting today.

A lot of the work that we do we would call something like a program evaluation where a government agency institutes a new program or policy and we come on board to evaluate, for example, the cost-effectiveness or the impact of that evaluation.

And typically program evaluation as it is labeled that way would be exempted from the research regulations.

Now in some cases that evaluation is merely obtaining some kinds of information from the program itself, evaluating it, synthesizing it and coming -- putting together some recommendations or a synthesis of findings about, you know, what is going on with that program.

In other cases we are provided information sometimes linked to a person's name and address and other identifiers, sometimes not, where we have confidential information about that person and that research is not necessarily reviewed by an IRB and those participants do not necessarily give informed consent to be part of this evaluation.

And I think what needs to happen is in some cases I would feel like, yes, that should have been reviewed by an IRB depending on the subject matter and the information that is being obtained. In other cases it is a very, very minimal risk situation where you could easily make the argument that it should not be reviewed.

So there is sort of the risks and the benefits for the individual to consider in weighing this determination and then there is a larger issue.

And I think the larger issue is what are the impacts on the participants in the program and larger

society if these evaluations are not done, if we are not able to answer policy questions about what these programs and policies are doing.

And if you think about adding the burden of additional IRB review and additional informed consent into the context of these programs that could actually have an adverse effect on the program itself. And an example that we talked about would be something -- thinking about a WIC program for women, infants and children. If all of the participants in a new WIC program or who are, you know, newly involved in WIC because of a policy change have to provide informed consent, for example, or do a release of information, or if somehow that type of research has to be reviewed by an IRB, is that going to adversely affect participation in the program and that kind of thing.

So I am not saying that there is a straight forward answer to this. I think it is a very important question to be asking because I think in some cases that IRB review and informed consent should be required for some of these programs and policies. I mean, some of the research on the programs and policies.

In other cases, I do believe that the risk is minimal enough where you are not adding additional protections and probably may not be worth the

additional burden placed on the research and the program.

I know I have kind of rambled on a little bit there but if you have any questions about it.

DR. SHAPIRO: I do have a question about that. I just want to clarify in my own mind what it is that you have just said. Obviously there are cases where informed consent can be waived when things are minimal and so on even if you are subject to a formal IRB oversight, if not review by a committee. I certainly understand that and for good and sufficient reasons.

But I have never really quite understood why someone who is doing an evaluation for internal purposes, evaluating let's say an ongoing program of some kind, you might think that the whole thing is exempt period vis-a-vis a researcher who does the exact same thing with the exact same information and exact same set of risks that should be treated differently.

I do not think you have suggested that but maybe you did. I just want to clarify it.

MS. COLETTI: No, I do not suggest that all. I think that the same regulations should apply to whoever is doing the research.

DR. KAUL: I would like to add to what Anne was saying. I think any time when Abt IRB is reviewing

something and they are unsure about something, I think it works pretty well for us, they involve our clinical trials division to give them some feedback whether this is clean or is something that should be discussed further.

And since in our clinical trials division I believe we operate under more stringent regulations we are able to help them out whenever we can and I think when you make the decision that it ought to be reviewed and what not, then we -- if they need me or somebody on my staff in the medical group -- function as a consultant to that Abt IRB in reviewing that particular application.

DR. SHAPIRO: Thank you.

Dr. Ross, could I ask you a question? You mentioned, and I certainly understand that depending on whether you are doing research here or abroad things may work out differently, you may have different kinds of procedures, different kinds of approaches are necessary in order to accomplish your work.

I am wondering if you can give me an example of that. I am trying to think about whether there is work that you do here that you could not do abroad or vice versa. If I could get some kind of feel for that in the area of the surveys and the analysis of large

datasets and things like that which you apparently are working on.

MR. ROSS: As I said before, I would consider that virtually everything we do falls into the category of minimal risk anyway.

DR. SHAPIRO: Yes, right, I understand.

MR. ROSS: The primary differentiations are that when you are doing this USAID funded research or other international research where we are essentially looking at issues of maternal and child health on child survival issues, the anemia studies, you cannot over play the voluntariness of their participation partly because the collaborating statistics agency in that country, the government of that country views this as a mandated activity for those who are participating or those who are selected.

Similarly, we are very careful here to make clear that having given consent does not mean that this consent is not revocable, and that at any time if you change your mind you can withdraw. We do not over play that either because that would cause a very high -- we believe it would cause a high degree of withdraw, because people believe that is what they are being asked to do.

Essentially we are trying to work with those -

- the governments in a manner that they consider to be appropriate without really compromising our own standards.

DR. SHAPIRO: Thank you.

Let me ask -- excuse me. Larry?

DR. MIIKE: But that is not -- that particular situation is not very different from here. If you are in a public benefit program in this country you are obligated to participate in an evaluation of it. I was just -- the part that I heard you earlier was that sometimes you feel uncomfortable about the kinds of more coercive tactics that a foreign agency would employ when you are working with them in order to get participation.

MR. ROSS: I think our greater concern in our involvement in DOD funded research is very limited, but I would say that is where our IRB had much greater difficulty where I think we are glad we have not had more to deal with because we could not reconcile that framework with the one that we are accustomed to operating in.

MR. McKENNA: Let me add to that. In some international work that we have been involved with as a support contractor to an intramural agency of the federal government that was working in collaboration

with a government agency in another country, and this would be a country where you might consider it relatively underdeveloped and where the standards are not the same standards of care that we have here, and I think it is fair to say that the monitoring using U.S. standards and using U.S. people is less than it is over there.

DR. SHAPIRO: Will, do you have a question? Will?

MR. OLDAKER: No.

DR. SHAPIRO: Let me ask a question which really asks you to think about this all in a slightly different way. In your own experience as you run up against the various rules and regulations that are -- you are required to comply with here in this country, are there aspects of that oversight system which are bothersome, counter productive, irritating, et cetera, that you think requires some change and everyone would be better off?

MR. McKENNA: Can I be first?

(Laughter.)

DR. SHAPIRO: You can be first.

MR. McKENNA: Well, in general, I think that we think that the system works quite well. There are some things that are perhaps in the details that from a

contractor's perspective do not work quite so well. Generally, when -- most agencies have IRBs, some do not. Some of those are aware that contractors have IRBs, some do not.

Program staff in agencies sometimes know that the contractor IRBs are involved here and are obligated to do certain things. Some are not so aware.

And when a contract is put together there is a determination made within the agency as to whether something should be exempt or not, so when it comes out to an organization like ourselves that has an MPA we take a look at it and make our independent judgment about it and the first question that comes up is: 'why are you people doing this."

There is -- often times there is agency review. There is a review by collaborating partners and when a contractor is coming in as a support -- in a support role often times having little or no -- sometimes having little or no involvement with the science or little or no involvement at even shaping the -- kind of the technical aspects of the work but -- and may or may not have a big role in informing the potential study subjects and trying to recruit them into the subject -- into the study.

The -- it would be -- I think it would be

helpful to have more sharing of information between the government and contractors and IRBs as well with more -- I guess bringing government people up to speed with respect to, you know, what the contractor's responsibilities are.

And then, I guess, on the other side is that sometimes when we are brought into these things and we have a very small role, maybe no role, some would say no role on some things, and yet the requirements if we decide that this is something that we have to take a look at, we do not take a look just at what we are doing, we have to take a look at the whole project.

And then we have to go out and either find the scientific expertise to bring in to review the whole project or we go to the agency and we try to develop a cooperative agreement under which that could be provided for us. And we try to do that as much as we can and we would like to do more of it.

DR. SHAPIRO: Let me just ask you a question. One of the suggestions that came up in the last panel and a suggestion we have heard before is that there are too many projects in which too many IRBs have to give approval, and that is just inefficient and so on.

If there were a system of accredited IRBs where we knew which IRBs were accredited and which were

not, would you feel satisfied that if an accredited IRB approved the whole project that you would feel after a quick review but you would feel satisfied that you did not have to use your own IRB or would that not give you any satisfaction at all?

MR. McKENNA: If there were a process in which we could participate on a trial basis and maintain our own IRB until we became comfortable with that, that would make a difference.

DR. SHAPIRO: Yes.

MR. McKENNA: If there were a process in which we could, you know, contribute to the IRB and not be held at an arm's length that would make a difference as well.

DR. SHAPIRO: Yes.

Alta?

PROF. CHARO: I would like to follow-up on that if I may because the -- I think there is absolutely widespread agreement that the redundancy of the system is a drain on everybody's time. The question is how one would accomplish some kind of streamlining.

Now with the previous panel I was asking questions about how one would anticipate a central IRB functioning when there are differences in substance in

the way in which the IRBs approach certain questions where reasonable people can disagree. Reasonable people and reasonable IRBs disagree on compensation language, on the inclusion of women and minorities at certain stages of the protocols, on the issue of disclosure of investigator's financial interests in the recruitment process, et cetera. I mean, the list is fairly long.

So now speaking as IRB chairs where your IRB has made decisions about how it wants to approach these questions, how would you find a system with a lead IRB -- how would you find a system that is most comfortable for you in terms of who selects the lead IRB, the degree to which the lead IRB is subject to appeals by the other IRBs that are buying in, especially in areas where it is not simply a matter of having tagalong studies and such but really there is a substantive disagreement that either needs to be resolved or you are out of the multi-center study.

Can you imagine a structure that would most accommodate your concerns for eliminating redundancy and at the same time not losing the ability to influence the structure of the protections that will be imposed?

DR. SHAPIRO: That is for anybody on the panel

who would like to answer that question.

MS. COLETTI: I do not think I can answer that question. I am not a member of Abt Associates' IRB, but I agree in principle that there is a lot of duplication and redundancy in the system.

One other aspect I would throw out and I think it will probably only complicate things is that we -- as an example, we work in a collaborative network now that is funded by the NIH with subcontractors through our company that are actually the clinical sites that do a study and we are in the position act the request of our client, the NIH, to review the informed consent forms and other materials that the IRBs have approved at our clinical sites.

And we have observed in some cases, and this is speaking mainly about academic IRBs, but it appears, and I have not obviously spoken with the people who represent these organizations, that a lot -- the institutions seem to review -- to perceive IRB review in addition to protecting human subjects as also protecting the institution in a legal or liability sense. And a lot of the things that the IRBs are asking to put, for example, in to a consent form or to clarify or to add to a protocol or other, say, patient information materials seems to be there more for the

protection of the institution than necessarily for the protection of the participants in the study.

So as you think about something like a central IRB or a lead IRB in a collaborative situation institutions may have issues with that because of the way they see what the IRB is doing for participants in the study as well as for themselves.

DR. SHAPIRO: Mr. Ross?

MR. ROSS: Very often we are involved in situations where multiple organizations are doing different pieces of a project. In situations especially where we are a subcontractor are doing work that is clearly survey research and is -- and could be considered exempt, if the prime contractor is funded, say by NIH, they may be adamant that we have to give them an assurance. And we will proceed to go through that process.

But we can very often get into a situation where another IRB expects much more -- much less than we would think is appropriate. Say a witnessed written informed consent for a survey of adults on nonsensitive information like that should not happen, but it happens. I do not think we are going to resolve this sort of thing without a whole lot of education of IRBs. People join IRBs and they are educated locally and are

basically falling into local traditions of what that IRB perceives its responsibility to be and I think that will continue without a whole lot of education and I do not know how you deliver that.

MR. McKENNA: I would like to answer that question by giving you the standard researcher's answer, and that is more research is needed and I think on an experimental basis. I think that the answer is not the same for every institution and every situation.

I would like to see a situation in which there might be some experimentation done in some settings with the notion of a central IRB and trying to foster input from the participating partners and support contractors to get it all as right, you know, as best you can. I think that is the best way to make progress on this thing.

DR. SHAPIRO: In your firms, those who serve on your IRBs, do they get any training? How do you satisfy yourself that the IRB members are doing what you would expect them to do?

MS. COLETTI: In our company the IRB -- as new members come on the IRB chair does some one on one training and also all members have done and continue to do training through OPRR and PRIMR and that is an

ongoing process.

We also are in the process of doing that same kind of training but from a different perspective for all of our project directors who work in the company so that they are more aware of what the issues are and what the IRB is going to be looking for and that kind of thing.

DR. SHAPIRO: Is that also -- is this some of your other experiences, the experience of other people here?

Yes, Bernie?

DR. LO: I would like to ask a follow-on question about how you run your IRBs. My impression from friends who have worked for firms like yours is that they have to do very careful accounting of their time and to whom it is charged to or what project it is charged to.

When one of your employees serves on the IRB or is vice-chair or chair, how is that allocated in terms of their support? Does the institution support that? Does your organization support that out of overhead costs or some other costs as opposed to the academic system where it is voluntary from the perspective of the IRB member? And questions, therefore, raised about whether they really are putting

the time in that it requires. I just wonder how you account for that.

MR. McKENNA: In our organization it is a part of the overhead and we expect people not to do it after hours. I mean, sure, they have to spend time after hours reading the materials that have been sent to them and studying up but it is a part of our normal operating expense.

DR. LO: And if I could ask real dollars and cents things. How much do you support people to say chair an IRB or to be a member of the IRB? I mean, can you give us some sense? I mean, I am trying to get a sense of what academic institutions ought to be putting in to supporting their IRBs in dollar terms.

MR. McKENNA: Well, we pay what some would say is a -- what the potential members say is a very, very modest amount. We pay outsiders $500 a day for the time that they put in and what we pay -- we give people in-house is they get no more/no less. It is just they are just asked to allocate their time to this or that.

MS. COLETTI: Our experience is very similar. It is an overhead cost that the IRB members, you know, the people who are employees, it is covered that way. I cannot give you direct information about how -- what level of effort each IRB member is putting into it.

The IRB meets quarterly and then also with ad hoc meetings as needed for projects that want to get started more quickly.

We could also give you information -- I do not have it here myself but there is a budget that is, you know, specifically set aside within the overhead pool for IRB activities.

MR. ROSS: My answer is different from the other two. We view the IRB activity as noncompensated time. We meet at lunch time. We buy lunch.

DR. SHAPIRO: Bernie?

DR. LO: If I could just say that because I think this is a big issue for firms not like yours, if we can come back to you at some point to help us get information on how this might be costed out say in an academic center that would be really helpful.

DR. SHAPIRO: An aspect of that that I am particularly interested in, and maybe this is a detail which you could explain to us separately, and you will forgive me if I do not fully understand how professional services are billed out and compensated for in your firms, someone who is spending time on an IRB is not spending time with a customer. Therefore, not generating revenue. Therefore, not doing a lot of things that are very valuable in this firm. At least I

believe they would be valuable.

How does a firm sort of deal with this in principle? I mean, you have a very valuable member who could be out there and getting the benefits of generating the revenue. How do you deal with that? How do the people think about it?

MS. COLETTI: In my opinion the company feels, and I think this is pervasive throughout the company, that the role of the IRB is critically important and that is why there is professional time set aside from other revenue generating things.

DR. SHAPIRO: I see.

MS. COLETTI: So that the people -- you know, they are saying -- for example, our IRB administrator, 25 percent of her time every month no matter what is set aside for IRB activities and, you know, so she is billing for revenue reasons 75 percent of the time to other clients, the company is paying for her time for at least 25 percent of her time.

DR. SHAPIRO: Thank you. That is very helpful.

Yes?

DR. KAUL: Just sort of adding further on that, from a revenue standpoint our organizations usually are -- we have a target bill-ability or charge-

ability.

DR. SHAPIRO: Right.

DR. KAUL: And, therefore, you try to maintain that pool and whatever is noncharge-able that accounts for the overhead and admin costs and IRB things so it does not impact the revenue. Hopefully, if your charge-ability where you want it to be.

DR. SHAPIRO: Steve?

MR. HOLTZMAN: Let's be clear if it is overhead it is billed into -- it is in the billing rate anyway from the people who are actually --

MS. COLETTI: I mean, the way -- Inder and I have -- we work in different parts of the company and, for example, when you bill out to a federal contract it is your labor time plus an overhead rate.

MR. HOLTZMAN: Right. But see my point was not to be critical of that practice. It is the fact of very simply that it is not as though there is a contribution of this time that would, therefore, act against companies wanting to do it. There is a reimbursement via either your indirect or your direct overhead rate.

MS. COLETTI: That is right. Everybody is paying for it.

DR. SHAPIRO: So there is no economic

disincentive to participate. That is what you are saying. That is what I was trying to get at and that is how it sounded.

MS. COLETTI: The only disincentive is one -- a company could choose to not include IRB costs in their overhead rate and take that out and then your IRB rate would be lower or you could put in something else as part of your IRB rate.

DR. SHAPIRO: I understand that.

MR. McKENNA: You are right about the fact that there is no economic disincentive. What we would like to see is that the other organizations, including the academic institutions, also get to the same position we are so that they put it into their overhead.

DR. SHAPIRO: Yes. It is understandable.

Now I think Abt has already mentioned that you use external IRBs. I was not sure if those were commercial IRBs or do you use external firms who have IRBs or professional? Which IRBs do you use externally?

DR. KAUL: Commercial IRBs.

DR. SHAPIRO: I see. Is that the same thing that you find yourselves in your experience using commercial IRBs at all?

MR. McKENNA: We have not done that. We have actually asked -- been asked to be a commercial IRB.

DR. SHAPIRO: I see.

MR. McKENNA: And we tried it once and it was not -- did not suit us and we would not do it. But we have not used commercial IRBs. We have often times teamed with academic institutions in which either -- and with other prime contractors or subcontractors in which it was determined that one or -- that a group not Westat might be the place where the IRB rested.

I would like to make a comment about the commercial IRBs and what I think is a real potential for us and that is that in surveys when you are trying to represent the entire population, let's say, of the U.S. small physician practices or clinical hospitals or organizations, whatever they are, come in to the sample in the same proportion to the, you know, extent they exist in the population.

And many times those groups do not even have an IRB and you would like to have them brought into the study so that you do not bias the study results. Taking them to a community group in an academic center and saying would you be willing to provide oversight to this organization is often times unsatisfactory and does not work.

And we think it is important to provide representation of these groups into the research and we would like to see some ways in which central or commercial IRBs, I am not sure what the difference is exactly, could be utilized effectively.

DR. SHAPIRO: Larry?

DR. MIIKE: A couple of questions. One on the overhead rate. What I hear is that, okay, you can put the IRB costs in an overhead rate but it is not easy to change the overhead rate so obviously it is not simply for us to say, well, you know, we should support IRBs more and you can do it through your overhead rate. Something has to give, right? So it is not as simple as that.

I want to know why you had problems with being a commercial IRB.

MR. McKENNA: It was not a project that we were invested in and we felt that -- if it is our project we are quite willing to put in the resources to do the job necessary to get on top of all the issues. If it is not our project -- maybe it is just a matter of mass. If we had, you know, 10,000 of these in an area and we could put them all together, certainly we might be able to get comfortable with all of the resources that we needed to bring to bear to do the

quality job but we were not there and we did not want it.

DR. SHAPIRO: Thank you.

Eric?

DR. MESLIN: Just a quick question about indirect costs and the like. The commission is either familiar with or will soon be familiar with the number of options that institutions face regarding payment for IRBs within the indirect cost rate and the 26 percent overhead that is now required is supposed to include IRB services.

I wonder if any of you have experience with or suggestions for the commission as to how it might be more efficient to resource IRBs, knowing that there are some current constraints on where funding for IRBs come from given that you have multiple relationships and have probably experienced a variety of ways by which IRB and review activities can be resourced.

Do you have any suggestions that you might in a sense wish to make that the commission might wish to suggest?

MR. McKENNA: I do not know what the 26 percent thing is.

DR. SHAPIRO: The 26 percent thing is what universities face with respect to the maximum overhead

rate for certain subcategory of indirect costs and it is capped at 26 percent and so this is where the IRB costs would fall into that category. Therefore, since most universities are already at the 26 percent rate for those administrative costs, adding new administrative activities means you cannot pass that cost on. I mean, that is -- I believe that is what you were referring to.

DR. MESLIN: Yes. Thank you.

MS. COLETTI: We have experienced a situation where an academic IRB will, in fact, charge the sponsor of the study for their review so they become like an academic -- I mean, like a commercial IRB in that case and it is usually a flat rate but that is one way where it is not directly coming out of the overhead pool where they could do that.

As that happens, you have to think about issues -- there is a lot of sort of financial conflict of interest issues that I think are happening particularly in academic institutions now where a lot of institutions are competing for research funds from federally funded, government funded and private sponsors.

And I mean think about bringing five million dollars for a new protocol into your program and, you

know, is it -- how hard or easy it is for the IRB to say -- to reject a protocol from a paying customer and that kind of thing.

So I realize that is a slightly different issue. It is like sort of the flip side of the coin there but to get back to your original issue, I know we are aware and have worked with IRBs that actually do charge a fee for their review to the sponsor.

DR. SHAPIRO: Yes, that financial conflict always exists within the organization, whatever their nature is, who is carrying on a project and doing IRB review at the same time. That is correct. That is something that is sort of built into the system as it currently exists right now.

Do you run across any other financial conflicts of interests that you observe in your work either with universities or with other organizations? Is that something which comes up often or hardly ever?

MS. COLETTI: It does not come up often but again going back to the one project I referred to where we subcontract with clinical sites. This is federally funded work but in collaboration with private companies that are developing the investigational products.

Some of our investigators do have financial interest in the companies of the product that they are

investigating and the new FDA regulations having to do with financial disclosure are addressing that but there are those financial things going on.

DR. SHAPIRO: Marjorie?

DR. SPEERS: The commission passed a resolution a couple of years ago stating that all individuals who are involved in research should have the protections of informed consent and IRB review. That means then that research, whether it is federally funded or not federally funded, should come under federal oversight.

If the federal regulations were expanded to the private sector, what would be the implications of that for companies such as yourselves?

Now I know that Westat has a multiple project assurance from DHHS, Macro International has a multiple project assurance from USAID.

Abt Associates, I think, does not have a multiple project assurance but uses the single project assurance mechanism for federally funded research.

MS. COLETTI: That is correct.

DR. SPEERS: So what would be the implications of expanding the federal oversight system to all research?

MR. ROSS: It depends on how you define

research and it -- our biggest issue, frankly, is we do a great deal of market research that we would never ever -- this is all exempt. It is straight survey research. There are no vulnerable populations. There is -- we give no thought right now to bringing that under the purview of the IRB and I cannot imagine doing that either. I do not know whether you are suggesting that.

If that were the case operating an IRB would be a full-time job. Being an IRB member would be a full-time job.

DR. SHAPIRO: Yes, Ms. Coletti?

MS. COLETTI: I would agree with that. What it means is that, you know, I would -- by sort of volume, about 60 percent of our work at Abt Associates is what we consider to be our government line of business and involves human subjects. Another ten or twelve percent is in our clinical trials group. That is all covered anyway but most of our work in the government business is in the program evaluation that I described earlier and it would definitely, you know, increase the burden on the IRB and again on the programs if you are talking about informed consent in a formal way, in a written documented way for all of those programs as well.

DR. SHAPIRO: Well, I think that you are right, of course, that the -- and something which we are in the midst of struggling with, it all depends how you define research or which activities fall into that category and which activities fall out of it, and one of the things that we are struggling with is whether we should take a rather broad approach to the definition of research and then increase the number of things that are exempted. So things that sort of automatically -- or you can go the reverse way around obviously and try to define those things first and have a narrow definition of research, and in that category exempt many fewer things.

So you are quite right to point to that. That is an essential aspect of this and something which is going to be central to our own discussions as we go ahead.

Thank you.

Any other questions the members of the commission have this morning?

MR. McKENNA: Let me just add one point to that.

DR. SHAPIRO: Yes.

MR. McKENNA: I would certainly agree with the other folks here that there -- for voluntary surveys

that are quite -- the level here is at a very low level that the issue of let's say privacy to me is -- well, the issue of recruiting people into this studies is -- I do not think there is a great risk here. However, there are many agencies in which they have protections of the confidentiality of the data and there are some that do not.

DR. SHAPIRO: Right.

MR. McKENNA: And if you are working for an organization that does, you do not have to be concerned so much about whether five years from now the data is going to be kept confidential as it is passed on from one researcher to another.

If you are working for a group that does not in some ways it would be nice if the agency had those protections then you could say, hey, we are very comfortable with this and we are going to be comfortable even after the responsibility passes from us to somebody else because at some point we are out of the picture.

DR. SHAPIRO: I think your comment hits -- and I thank you for it -- hits on a really very important point, which concerns either privacy or confidentiality and how strong the systems are in any particular situation to protect that and where those systems are

very strong you can proceed in one way with a great deal of confidence. If they are not, you would want to proceed in another way to provide the protections, and in some sense there is a trade off here.

And it is at least my own view -- I do not know how other members of the commission feel about this -- that that is an area where the current regulations do not do a very good job, either of counting them as protections or of encouraging confidentiality or systems that would protect confidentiality, as opposed to persons who in all cases come and go. So that is, I think, an extremely important point.

Steve, you had a question and then I think we will adjourn.

MR. HOLTZMAN: It is following up on Marjorie's question, which is maybe another way of trying to peel back the onion.

Since you folks can get sponsorship from both private and the fed, correct, and engage in a wide range of activities, think about your logic tree as you go through. I think what I am hearing, as you ask the question first, is this human subjects research; yes or no. If yes or if no, do you then ask a question who is the sponsor and as a function of who is the sponsor

treat it differently or is it treated uniformly when the determination is made of human subjects research, yes or no.

And, if so, then the issue of a sponsor or whether it is at an institution which has an MPA becomes in one sense irrelevant because I think actually if we could go back to the last panel that is what I think you will largely find is the question of sponsorship never really becomes salient.

MS. COLETTI: It is the same thing for us. Everything is treated the same regardless of sponsor.

I would make one point, though, and it has to do with our single project assurance. The way you obtain a single project assurance is through the contracting officer at the agency that is funding the research. If that contracting officer does not think that that research requires IRB review then that contracting officer will not put you forward to get the special project assurance.

This has happened to us on a particular project where our Abt Associates' IRB felt that they should be reviewing this project and they did but we never received a single project assurance for our review of that because the agency felt that it was not required.

DR. SHAPIRO: Let me thank you all very for being here. I will refrain from asking which pool of costs your time went to this morning, but we really are very grateful to you and I hope you will not mind if we get back to you with some specific questions as our work goes on but thank you very, very much for being here today.

MS. COLETTI: Thank you.

DR. SHAPIRO: Gentleman and ladies, we are adjourned.

(Whereupon, at 11:59 a.m., the proceedings were adjourned.)

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