20th meeting of the National Bioethics Advisory Commission (NBAC)

Hilton Hotel

Tysons Corner, VA

MARCH 3, 1998 and MARCH 4, 1998

DAY ONE

DAY 2

DAY 1 - CALL TO ORDER – 1:20 P.M.

WELCOME AND OVERVIEW OF AGENDA - Dr. Harold T. Shapiro, Commission Chair

DR. SHAPIRO: First let me extend a welcome to all my fellow Commissioners and to those members of the public who are here today, and also to those speakers who have been invited. As far as I know, only Jim Childress and Steve Holtzman are not scheduled to be here this afternoon. They'll both be with us tomorrow. I think Diane (Scott-Jones) should be here shortly. I believe she's scheduled to be here this afternoon—that's our impression. She's not here right now but she'll be here momentarily. I saw her just a few moments ago.

Our meeting will run the rest of this afternoon and all day long tomorrow. And there really are, as you can tell from your agenda, three parts to the meeting. One will be a discussion of particular international issues; then there will be a discussion of the report on human biological materials, which will take a lot of our time both today and tomorrow; and then there will be a discussion of the report on disorders affecting the decision-making capacity. That will not come until tomorrow afternoon. So I hope as many Commissioners as possible will stay through tomorrow afternoon because that report is getting ready to be put out in some interim draft form, and I'm very, very anxious to have everyone's input on that. And you can see the latest draft at our next meeting.

As I said, we have a lot of our time, the bulk of our time perhaps, devoted to the human biological materials because there's lots of work still to be done on that issue and I'm anxious to move that report along. I want to thank both Tom and Jim for accommodating their mutual schedules to enable this agenda to be set forward the way it is.

Now, the first item on our agenda I'll come back to in a few moments. First, I'm going to ask Eric to say a few words, and then we'll go to the international research issues. And in that context, we have three people who will be addressing us this afternoon and then we'll follow that with discussion. I'll get back to more details of that in a moment. Let me now turn to Eric to see if he has any items to report on.

Eric?

EXECUTIVE DIRECTOR'S REPORT - Dr. Eric M. Meslin, Executive Director, NBAC

DR. MESLIN: Thank you very much. The only thing I want to bring to everyone's attention is that we are in the fortunate position of continuing our effort to add to our staff at NBAC, and, although she's not here today, Debra McCurry has joined the NBAC staff to take on the responsibilities for our infomatics and resource capabilities. Debra had a similar position at the Presidential Advisory Committee on Gulf War Veterans' Illnesses, and we're delighted to have her.

I should also let the Commissioners know, as well as the public, that the staff has undertaken a concerted effort to completely understand its responsibilities with respect to the national archives. Our filing capabilities, as well as our resource capabilities, are being brought up to speed. So I'm delighted to inform the Commission that our continuing efforts to increase the quality and the quantity of our staff is proceeding apace and hopefully we'll have more announcements at future meetings. That's all for now.

INTRODUCTION TO INTERNATIONAL RESEARCH ISSUES AND SPEAKERS - Dr. Harold T. Shapiro

DR. SHAPIRO: Thank you. As I mentioned a few moments ago, the first item scheduled for this afternoon is the focus on some international research issues. If you recall, the Commission first heard testimony on this issue from Dr. Wolfe; I don't remember if he was the first, but it was last July when we first heard testimony on this issue and indicated at that time in the coming year that we would put that on our agenda; that we would, in fact, take up that issue. We revisited the issue very briefly at our meeting in Los Angeles, roughly a month ago, again deciding that it was now time to turn our attention to this issue.

I think it's important to note at this time that we've not yet fully decided on the scope of the issues that we wish to address in this area, but we hope to hear from various experts, build a better understanding of the scope of the issues, and decide which ones seem most important and most effective for us to deal with. I would say that at this time we're sort of in the formation process of trying to decide the scope of our agenda and just which subjects we ought to be addressing.

We're going to hear from three speakers this afternoon who certainly can provide us with background

information and some of the rules that U.S. researchers must abide by when conducting research in other countries, and what some of the international instruments are and how they affect transnational research and so on. We're really very delighted and privileged to have the speakers who will be here this afternoon.

So let me turn directly to them. We're going to have a somewhat different order than indicated on your agenda because of plane arrivals and departures, etc. Professor Dickens is not yet here, but I understand he should be here at any moment. His plane arrived at 12:40 and he should be here in plenty of time. If it's all right with our guests, we will proceed by turning first to Duane Alexander, then Thomas Puglisi.

The Commissioners have been provided with biographical sketches of our speakers, let me just say an additional word right now. First of all with respect to Duane Alexander, he's Director of the National Institute of Child Health and Human Development, and he will talk to us from the perspective of a researcher with a long history in the international domain. Dr. Alexander, we're very, very grateful to you for taking the time to come and address us this afternoon. Thank you very much and welcome.

INTERNATIONAL RESEARCH: A RESEARCHER'S PERSPECTIVE - Dr. Duane F. Alexander, Director,

National Institute of Child Health and Human Development (NICHD)

DR. ALEXANDER: Thank you very much. It's a pleasure and a privilege to appear before this group. I'm going to discuss in a relatively brief fashion, why international research is a topic of concern, give you some idea of the scope of NIH's international research activities, talk briefly about some current issues in the international research scene, and make some mention of the role of international guidelines and the role of the United States in that process.

If we look first at why international research is a topic of concern, we can really look at it from three different perspectives. First is the scientific imperative, if you will. Scientific solutions to such problems as communicable disease, unsustainable population growth, environmental health, and famine require a coordinated global response. Public policy decisions of national and international dimensions require thoughtful assessment of the scientific data that's collected through international efforts. I think the scientific imperative is pretty clear, and as that's not the major focus of your interest I won't say much more about that.

The second, if you will, might be a self-interest imperative. From the self-interest standpoint, the direct and secondary consequences of the health status of developing nations on the American public are significant. Consequences include the spread of new pathogens, deforestation, worsening pollution, mass migrations, and diversions of our national revenue for humanitarian and emergency aid. Thus, it could be argued that self-interest should reinforce our efforts to mobilize the world's scientific talent to address the special health needs of three-quarters of the world's population who live in developing countries.

Third, there's also an ethical imperative. This ethical imperative is built not on self-interest, but rather on concerns for beneficence and justice. Here the arguments remain compelling. The health problems of developing nations constitute only 5 percent of the world's expenditure on health research, but these countries suffer 93 percent of the burden of premature morbidity and mortality. Acute respiratory infections result in 7.4 million deaths a year in developing countries predominantly. Diarrheal diseases also—5 million deaths, predominantly in developing countries. Complications of pregnancies present significant maternal and perinatal risk and are estimated to be responsible for half a million maternal deaths a year. That is in contrast to about 300 in the United States. The burden of parasitic infection also constrains economic development through the loss of significant productivity.

These public health problems are exacerbated by population pressures. It increases disease burdens and exceeds health care capabilities. Thus, if we're truly concerned for our fellow men and women, we're obliged to direct resources to improving their health and their well-being. So how do we do this mechanistically and ethically? For whichever of these three reasons, we have found a way to do so through our international programs, and I'll talk primarily about the NIH's approach in these international activities.

International programs are conducted as a direct extension of the domestic health mission of the NIH. Support for these activities is broadly provided for across the NIH through research grants and contracts, through fellowships, scientist exchange programs, and international agreements. The Fogarty International Center, one of the major NIH divisions, serves as an organizational focus for international activities and supports international programs through its legislated mandate.

The NIH awards grants and contracts to foreign investigators under provisions of the Public Health Service Act of 1944. Before a foreign grant is made, all applications for such a grant have to be individually reviewed and approved by the national advisory councils of the awarding institution, and they also must take into consideration whether identical studies could be conducted in the United States. If they could, they may not recommend awarding that particular grant to a foreign country. Also, the proposal must fall in the top 50 percent of priority scores for approved applications. This isn't usually a problem since essentially everything we fund falls into that category .

I should also note that the average funding level for foreign grants is less than half that of domestic grants, in large part because labor is cheaper in foreign countries, but even more so because foreign institutions are ineligible for indirect costs. So there's no indirect cost applied to foreign grants, which consumes about a third of the total cost of a grant awarded in the United States. We should also note that except for the Human Frontier Science Program of the "Group of Seven" and the Commission of the European Union, and grants that are made from funds supplied by countries to those programs, the United States is the only country that makes grants to scientists in other countries.

I want to use a little different type of visual aid. Instead of slides, I invite you to turn to the NIH Annual Report of International Activities that is at your desk. If you would open to page 3 and look at the table that's there, or Figure I.1, this gives a graphic display of the distribution of NIH's international funding in Fiscal Year 1996. The total was about $195 million, representing 1.8 percent of the NIH's budget.

In recent years the dollars have risen, but the percentage has been unchanged over the last fifteen years; about 1.8 percent overall, with about half of that amount provided in grants and contracts, and most of the rest provided in fellowships for foreign scientists to receive training and conduct research at the National Institutes of Health intramural program. About a third of the NIH's intramural scientific staff is in this international exchange program. They receive superb training, then take these skills back home. The other half is for research awards.

If you will now turn to pages 3 and 4 and look at Table I.2, this provides more detail on the expenditures in this program. It might be easiest to focus on the Total Column at the right. Again, you'll see that the grant dollars are evenly divided into two categories, the first two lines. First is the grants that are made directly to investigators in foreign countries, constituting about $32.9 million.

PROFESSOR CAPRON: Excuse me. Could I just ask a question?

DR. ALEXANDER: Yes.

PROFESSOR CAPRON: Would you like us to hold our questions, or would you like us to, if we feel it necessary, interrupt as you go through?

DR. ALEXANDER: If you feel it's urgent, please interrupt as I go.

PROFESSOR CAPRON: So "urgent" is the criterion?

[Laughter.]

DR. ALEXANDER: Otherwise, it is probably smoother to go ahead with it. But if you have a burning question and it's about something that's on that page, let's do it now.

PROFESSOR CAPRON: Thank you. No, questions.

DR. ALEXANDER: Okay. So about $32 million, then for research directly provided in grants to investigators in other countries. And then the other foreign component is about $36.9 million, which is awarded as a foreign component to a domestic grant. This is an applicant from a United States institution that has a foreign component as part of what they will do. This has been the largest and fastest-growing component of this grant activity; it has tripled since 1989, and I'll get to the reasons about that in a minute.

If you'll turn to pages 6, 7, 8, and 9, and probably look primarily at page 9, Table 1.3, this provides the distribution of these dollars by country. You can see, if you're interested in that amount of detail, which countries get what kind of support. In summary though, it shows that 184 research grants worth $32.8 million have been awarded to investigators in foreign countries. If you look at the subparts of that table, you'll also note that half of the grants, 99, go to investigators in our neighbor to the north, Canada; 18 to the United Kingdom (UK); about 16 to Israel; and then other countries tail off after that. So most of it is to Canada and the UK.

In the next vertical column you will notice that foreign components of U.S. grants, again, account for 572 different grants for nearly $40 million. This is an especially dominant mechanism for a developing country that has difficulty competing on its own with the U.S.-based investigators. So this has been a rapidly growing program. There has, in fact, been a modest decrease in the total numbers of grants awarded directly to scientists in other countries because of the competition, and this more effective strategy has been a collaborative proposal with the U.S. investigators. If the proposal is awarded, NIH provides funds to the U.S. institution, which is responsible for carrying out both the domestic and the foreign components of the proposal.

This has been a particularly effective way to collaborate with developing countries. The NIAID—for example, biology and infectious disease—currently supports special international programs in such areas as tropical medicine, tuberculosis, and HIV/AIDS. Over 70 percent of NIAID's specialized research and training programs go to either developing countries or democracies of the former Soviet Union.

So that gives you kind of an overall picture. If you're interested in more detail, the rest of this report provides brief summaries of almost every project that's underway. You may want to give some attention to that at your leisure.

PROFESSOR CAPRON: Dr. Alexander?

DR. ALEXANDER: Yes?

PROFESSOR CAPRON: For the record, the research going on in Africa and Thailand on AZT for pregnant women, was that NIAID?

DR. ALEXANDER: Some of that was CDC. The two recent studies reported were both CDC studies. But there are studies supported by NIAID and NICHD in developing countries on related topics.

PROFESSOR CAPRON: And the CDC funding is not included in this report?

DR. ALEXANDER: That's correct. This is just NIH.

When you do have a chance to review this fuller report, you will see that the scope of international research is enormous and basically contains pretty much the same kind of scope of activities that are done domestically, plus research on diseases that don't occur in the United States. It is important to remember that we're not just talking about developing country research in international activities, but research done in fully industrialized countries of Europe, Asia, Canada, Australia, Israel, and elsewhere.

Not only do we have the same kinds of research, but, as you will hear in a little bit from Tom Puglisi, we also have NIH and Public Health Service guidelines for doing research with human subjects that follow the dollars if they are from the Federal government. We also have FDA rules that apply to nongovernment funds if the data will be submitted to the FDA in support of a licensing application.

Thus, if we're doing genetic studies in a large cohort in South America, the same privacy issues pertain. If we're doing a vaccine study in Europe or Africa, the same issues of an appropriately treated control group apply. If we're doing a contraceptive study in Asia, the issues of dealing with controls and with contraceptive failure have to be dealt with. And when the NIH implements its new policy requiring the inclusion of children in research, unless there's a good scientific reason for excluding them, this will challenge existing policies in Europe as much as elsewhere. Even in the most recent document from Europe, the Council of Europe's Convention on Bioethics, the approach to children and others who cannot give full informed consent themselves is to exclude them from research unless countries make specific provisions in their national law to include them. This really contrasts with the U.S. approach of inclusion along with everyone else, but providing special additional protection for these individuals.

DR. SHAPIRO: I have a question here.

PROFESSOR CHARO: A similar issue arose several years ago about the inclusion of women of reproductive age, and NIH then adopted a policy favoring inclusion against the backdrop of exclusion. My understanding from France, in particular, and a couple of other European countries, is that the standard there was still an exclusionary standard. What experience did NIH have in implementing its new policy of inclusion of fertile women when they then tried to export that to transnational research collaborations?

DR. ALEXANDER: I wish I had data on that, but I don't. I'm sorry. We can try to look at that and get that

information back to you specifically, but I don't know. It's new enough a policy that we may not have a whole lot of experience with it yet. But I will check and see what I can find and get that back to you.

PROFESSOR CHARO: I'd much appreciate it. Thank you.

DR. ALEXANDER: What really does differ is the general standard of care from country to country which, as we've seen from the HIV/AIDS maternal-infant transmission studies, can be a source of conflict. This brings into focus the discussion that Professor Dickens will be presenting on existing international documents and the protections that they provide. One problem with these documents is that they sometimes can be reinterpreted by people to suit their own ends, as happened in one case with the Declaration of Helsinki, which was reinterpreted by some to require the standard of care in developed countries to be used for studies in developing countries.

This misconstrual of the intent of that document was pointed out in a letter from Professor Pavl Riis of Denmark to Dr. Harold Varmus at the height of the controversy. Professor Riis wrote, "public citizen points to the 1974 Declaration of Helsinki," and quotes the sentence, "every patient, including those of the control group, if any, should be assured the best proven diagnostic and therapeutic method." Professor Riis then says, "as one of the three Nordic authors of the Declaration of Helsinki and consequently of the sentence, I must emphasize that to any knowledgeable reader it is implicit in a global perspective that this means `in accordance with national accessibility.' Thus, the analogy to the Tuskegee study is without meaning."

Unfortunately, we don't always have the original authors of documents around to consult regarding their intended meaning, nor would, for example, James Madison necessarily agree with what today's Supreme Court says about what the Constitution that he wrote means. Thus, it is important that we have international documents periodically reviewed and updated by international groups.

That brings me to my final point. I don't know what the Commission projects as its role in this arena, but to me it would seem that rules and guidelines for international research are best developed by international bodies with participation as broad as possible. The U.S., through NBAC or any other organization, is one player, although a highly influential one, on the world bioethics stage. We can be a valuable resource or conduit of information and even play a lead role, for we have much to offer. But in no way are we a solo or dominant act. A concern at present is that there are a number of international groups vying, if you will, for a primary role in this process. Sorting out these competing roles is a major challenge that perhaps NBAC can help to resolve without entering into the field as yet one more competitor.

In conclusion, I hope this information and perspective are helpful to you as you address this important issue. I'll be glad to answer any questions.

DR. SHAPIRO: Thank you very much. Let me turn to the Commissioners first. Mr. Capron, then Dr. Lo.

PROFESSOR CAPRON: Duane, two questions. The first is, the Fogarty volume you mentioned indicates there is roughly $200 million of U.S.-sponsored research throughout the National Institutes of Health.

DR. ALEXANDER: Right.

PROFESSOR CAPRON: And about half of that is spent abroad and the other half spent for training foreign doctors and so forth in the United States. So we're talking roughly $100 million. Could you help me to understand how that compares with other spending, specifically U.S. government spending through other branches of HHS, or through DOE, DOD, etc. if you have knowledge there, and if you have any sense of how it compares to pharmaceutical or other private research funds for studies by U.S.-based companies or multinational companies in other countries?

DR. ALEXANDER: I don't have figures on expenditures of other agencies, either in HHS or Defense, for research in other countries. Perhaps someone here from the FDA might provide an indication of drug company investment in research in other countries. I think the FDA has a policy of requiring at least one domestic study but they will accept data from other countries.

Can anybody from FDA comment on whether they have information on expenditures of pharmaceutical companies overseas too? Nothing? No data? I'm afraid we don't have that.

PROFESSOR CAPRON: I would hope that in light of any report we're going to do on this that we would—it doesn't have to be through testimony, but through speaking to PHARMA, whatever the other groups that would know

that, just orders of magnitude, not dollars and cents, as to who would be affected by any recommendations potentially if there were any modifications that come out of our recommendation.

The second question takes up on your comment of the relative status of the United States in this area as an international player, but not a superpower as we may be in other spheres. You have been the U.S. contact with the Council of Europe, their ethics activities. I understand we were provided with the convention in draft form but it has been promulgated last April. As I understand it—I went to the web site the other day and I can turn this into staff—there are 22 signatory nations. It is open to signature by non-member states of the Council of Europe who have participated in the drafting process, and that includes the United States, as I understand it.

DR. ALEXANDER: That's correct.

PROFESSOR CAPRON: Has there been any official review of this document as something to which the United States might become a signatory?

DR. ALEXANDER: Not in an official way. I have had communications with people at NIH and with the State Department regarding this document and the possibility of the United States becoming a signatory to it. Though there are now, I think, 26 countries that have actually signed, only one, so far, has actually ratified it through its national parliament or assembly.

There are significant differences in this document from the United States' policies and procedures, from the protection of human subjects guidelines. I mentioned just one example: the differences in participation of children or other persons who can't give consent in research. There are a number of things that, if we were to sign this document, we would have to make a commitment to significantly change our policies and procedures.

I can provide, if it would be the Commission's wish, a list of those differences in our policies that are certainly inconsistent with what is required in the convention.

DR. SHAPIRO: That, in fact, would be very helpful to us. We're trying to understand just how our tentative views on some of these subjects relate to what's going on elsewhere. So if you could do that, it would be very much appreciated.

PROFESSOR CAPRON: Right. Do you have sort of like a crosswalk that puts together —

DR. ALEXANDER: Yes. I published an article with Bill Dommel in the Kennedy Institute of Ethics Journal last year, a summary and a side-by-side comparison, really, of U.S. provisions from NIH and FDA, and comparing this with the provisions of the convention. If the Commission does not have that, I can make reprints of that available to you as well.

PROFESSOR CAPRON: Perhaps it would be useful, once we've had a chance to go over that, to ask Dr. Alexander to come back with us, because the specific mention you made of the children's provision was not one of those that I thought was that different, and so I'm obviously missing something. And rather than taking our time now, I'd be happy to hear more about that.

DR. SHAPIRO: Dr. Lo?

DR. LO: Duane, I wanted to ask you to comment on what you think NBAC'S role might be as we begin to tackle this very important but also very large topic. You gave us a few suggestions, such as warning us about acting unilaterally in international issues. But are there issues you think that NBAC could play a special role in on this large issue of international research?

DR. ALEXANDER: Well, I think you'll probably be able to have a better feel for this after Bernard Dickens' presentation when he talks about some of the international documents and perhaps gives an update on the status of some of the activities that are going on with regard to revisions in existing ones or developing new ones on the part of the U.N., of CIOMS, of other organizations. Clearly, I would think that there is a role for the U.S., probably through NBAC, in these activities as a partner with other countries in helping to make sure that the views of the U.S. are represented in these documents and that they are written as clearly with respect to intent as is possible to do for an international document.

Again, I think that the role for the U.S. and for NBAC is as a partner with other countries in these international

activities. There also is probably a role in assuring that the U.S., as it gets involved in activities in other countries, does adhere to the basic principles that underlie research here and should underlie that research abroad as well, taking into account differences in setting that do occur but making sure that work that is done is acceptable and something that we can be proud of.

DR. SHAPIRO: Thank you. Alta?

PROFESSOR CHARO: Just a couple of procedural questions. When it comes to deciding whether to be a signatory to something like this Council of Europe statement, is there the possibility of reservations so that one can become a signatory to all but a few identified provisions?

DR. ALEXANDER: The ratification document part of the Council of Europe's convention allows for reservation to specific parts only, primarily reservations with regard to embryo research, and only for countries that already have differing national laws at the time the convention was passed.

PROFESSOR CHARO: Okay. The second question is, within the U.S. government, obviously, there is going to be consultation about whether to become a signatory, but in which agency or which department does the real decision get made about whether to become a signatory?

DR. ALEXANDER: I believe that is in the State Department.

PROFESSOR CHARO: Thanks.

DR. SHAPIRO: Thank you.

PROFESSOR CAPRON: It's a treaty, which the U.S. as a policy does not go out of its way to seek signing.

PROFESSOR CAPRON: I will pass up to the Chair—I printed it yesterday when I was preparing for the meeting—the Council of Europe's chart of signatures and ratifications which shows, as Dr. Alexander mentioned, that only Slovakia has actually ratified the document, although there are 20-some signatories recorded here, all going back to last April when the document was first put forward. They are mostly the smaller countries of Europe.

DR. SHAPIRO: Thank you very much. Any other questions for Dr. Alexander?

First of all, thank you very much. I hate to impose on you. If you can stay, it would be more than welcome and you might be able to help us with some of the underlying discussion.

DR. ALEXANDER: I'd like to stay for the rest this discussion. Thank you.

DR. SHAPIRO: It's very much appreciated. Thank you.

Let me turn now to Tom Puglisi, Director of Division of Human Subjects Protection, the Office for Protection from Research Risks, better known as OPRR. He will talk to us about issues relating to the protection of human subjects in international research funded by the U.S. government; in particular, mechanisms to contract with foreign institutions.

Thank you for coming. It's a great pleasure to have you here.

BASIC PROTECTIONS FOR HUMAN SUBJECTS IN INTERNATIONAL RESEARCH -

Dr. J. Thomas Puglisi, Office for Protection from Research Risks (OPRR)

DR. PUGLISI: Thank you very much and thank you for inviting me. As you all know, I'm from the Office for Protection from Research Risks (OPRR). And I'd like to point out to you before I start that there is a handout that you were given both in your briefing books and today that looks like this. It is a front page with bullets. The handout itself consists of the first page and then there is an example of an assurance document to which I'll refer as I speak.

I believe that I've been invited here today because the Commission recognizes that the Department of Health and Human Services and, particularly, the National Institutes of Health, is a principal player in the funding of international research by agencies of the United States government. But I would like to point out, as Professor Charo has pointed out, that HHS and NIH are not the only players in this arena. So I will limit my remarks today to the enforcement of the Health and Human Services regulations for the protection of human subjects, the HHS regulations, and I can't

speak for either the implementation of the Federal policy or common rule by other Executive departments and agencies, nor can I speak to research that may be conducted by other agencies of the government that are not signatories to the Federal policy, and I cannot address the issues related to international research that would be related to the approval of drugs, devices, and biologics. Those would be FDA's purview. I would recommend that as you get more deeply involved in this area you also think about the issues that FDA would raise related to international research.

So what we're going to talk about then is the HHS regulations, the enforcement of the HHS regulations, specifically 45 CFR 46. The bottom line here, and I could deliver a very short talk , as you see on the slide behind me, all sites, both domestic and nondomestic, must comply with 45 CFR 46. They must comply with the HHS human subjects regulations if the research is conducted or supported by the department. There is, however, one exception. The regulations provide that the department may publish a determination in the *Federal Register* that international research will be conducted under a national procedure or a local procedure that provides at least equivalent protections to the HHS regulations. The regulatory phrase is "at least equivalent protections."

To date, OPRR has published no determinations of equivalent protections. We have not found any national code to offer the same level of protection that the HHS regulations provide, particularly in terms of the enforcement mechanisms in provisions of HHS regulations. Most of the national codes that we have been asked to review have offered protections that are voluntary or advisory but do not have the kind of enforcement mechanism that the HHS regulations have. As a result, we have not made any determinations of equivalent protections.

To review for just a moment: You will recall that the regulations provide three core protections for human subjects, the first being review by an Institutional Review Board. IRB review consists of review by a board of at least five members made up of both men and women. The five-member board must include at least one scientist and at least one non-scientist, who must be present at the convened meeting at which the research is discussed, and must also include one member who is otherwise not affiliated with the institution conducting the research.

This same standard is expected whether the research is conducted in the United States or in another country. And in reviewing assurances provided by institutions conducting HHS-supported research outside the United States, we enforce this same standard of protection. We look for an Institutional Review Board that has five members, scientists and non-scientist, and unaffiliated member.

The second of the core protections provided by the regulations is the requirement for informed consent, the legally effective informed consent of the subject or the subject's legally authorized representative. You will probably recall from the very first meeting of the Commission, Gary Ellis (the Director of OPRR) outlined for you the eight required elements of informed consent that are listed in the regulations. These eight required elements must be present whether we're talking about domestic research or international research.

Notice, however, that there's one additionally complicating factor relevant to international research. The definitions of legally effective and legally authorized will depend in part on relevant law in the jurisdiction in which the research is conducted. So that just as these terms may vary from State to State within the United States, they will also vary from country to country in international research. In order to have legally effective informed consent in HHS-supported international research, the informed consent must include the eight required elements and be in compliance with local or national law.

The third of the core protections under the HHS regulations is the requirement for an assurance of compliance. An assurance is a written agreement approved by OPRR provided by the institution to conduct the research, pledging that it will comply with the HHS regulation 45 CFR 46. OPRR accepts and uses several different kinds of assurances, which I'll describe in a moment, but every assurance has to include several basic elements.

First, there must be a statement of ethical principles. Those ethical principles must guide the conduct of research at the institution providing the assurance, and the ethical principles must apply regardless of whether the research is funded by HHS or funded privately or by the institution. Most domestic assurances cite the *Belmont Report*, with which I'm sure you're all familiar, as the statement of ethical principles to which the institution subscribes. Many international assurances cite some other statement of ethical principles, most commonly the Declaration of Helsinki. Occasionally, an international assurance will cite a national policy or a national statement of ethical principles. That is certainly acceptable as well.

The assurance must also include the designation of an Institutional Review Board with a membership roster. The Institutional Review Board in international research is often called something other than IRB. In Europe, for instance, it is commonly called an ethics committee. In other places it may be called something else. What the board is called is immaterial, as far as the assurance goes, and as far as protections for human subjects go. What is important is that there is a body that is configured in compliance with the regulations that will review and have oversight authority over the research to be conducted.

And, finally, the assurance must describe, at least to a minimal degree, the procedures that the IRB will follow and the reporting procedures that will be used for reporting to OPRR on anticipated problems involving risks to subjects or others, or the suspension or termination of research, or noncompliance with the assurance, or the IRB's determinations, or the regulations. These documents may be modified to some degree to fit the particular needs of the institution involved, but most assurances follow our sample documents fairly closely.

There is, however, one exception that's important for international research. International assurances often incorporate specific protections for human subjects in lieu of repeated citations of 45 CFR 46, in lieu of repeated citations of the U.S. regulations. If any of you are familiar with the assurance documents that your home institutions have provided, you will know that 45 CFR-something is mentioned probably five, ten, to fifteen times per page in that assurance document. This is something that we do not require of international institutions when they are providing assurances. Although some institutions are certainly willing to use the same sample that we would expect from a domestic institution, international institutions have the option to use an assurance that simply states and describes the protections that they will enforce rather than repeatedly referencing HHS regulations.

We have essentially three kinds of assurance documents that we use in assuring HHS-supported research. The first is called a multiple project assurance, or simply MPA. An MPA covers all federally-supported research that is conducted at the institution over a period of time, usually five years. We currently have roughly 450 institutions that have been awarded MPAs by OPRR. Only one of those 450 institutions is a non-U.S. institution. We have one Canadian institution that has successfully negotiated a multiple project assurance with us. That assurance, by the way, looks pretty much like the other 449 assurances that we have received from domestic institutions.

The second kind of assurance that we use is called a cooperative project assurance, or CPA. A cooperative project assurance covers participation in certain HHS-supported multicenter, usually multi-trial, research. It covers what we call participation in a cooperative protocol research program. What is a cooperative protocol research program? It's a program in which there is significant oversight of protocol development and sample informed consent language by the HHS funding agency. Examples include the National Cancer Institute's clinical trials program and the Centers for Disease Control and Prevention's international initiatives.

A CPA is like a multiple project assurance except that it covers participation only in the designated HHS-supported multiprotocol research programs that OPRR has recognized. A copy of an international CPA is attached to your handout. If you look at the language in that CPA, you will see an example of what I meant a moment ago when I said that we can accept an assurance from an international organization or group that simply describes the procedures that are in place rather than citing the regulations over and over and over again. We currently have about 1,500 cooperative project assurances, about 125 of which are with institutions outside the United States.

International CPAs often include multiple sites. For example, the Cancer Research Campaign (CRC) in the United Kingdom is a single assurance that actually covers 19 individual sites that participate in the CRC. The EORTC, the European Organization for Research and Treatment of Cancer, has an assurance that covers 110 sites. One single assurance covers the 110 sites spread out all over Europe that participate in the EORTC. So we have a significant amount of international research of primarily a clinical trial nature, or a CDC initiative that is taking place at multiple sites throughout Europe and the rest of the world.

Finally, we have a document called a single project assurance. As the name implies, a single project assurance, or an SPA, applies to a single HHS-supported research project. For research covered by a single project assurance, OPRR actually reviews the informed consent document and a summary of the research prior to granting the assurance. This is obviously not the case for an MPA or a CPA where the assurance covers many, many protocols.

OPRR currently has about 3,000 active single project assurances, including more than 700 active assurances in an international setting; 700 single project assurances from non-U.S. institutions. Historically, OPRR has negotiated

assurances in over 110 countries, on every inhabited continent. Some of those assurances use a sample document, a boilerplate that is virtually identical to that used by domestic institutions; other single project assurances use a document that simply describes protections for human subjects somewhat like the international CPA that I've given you. In either case, we believe the assurance provides a commitment by the institution to provide protections for human subjects that are in compliance with the HHS regulations.

This has been a quick overview of how OPRR enforces the HHS regulations in international context. I would be happy to try to answer any questions you may have about how we do what we do.

DR. SHAPIRO: Thank you very much. Laurie?

MS. FLYNN: Is it fair to make the assumption that given the scope of this research and the many other responsibilities that you at OPRR have that you're not able to do much in the way of site visits to follow up on any of this? Has there been any history of following up that might be helpful to us?

DR. PUGLISI: As far as I know, we have never conducted a site visit at a non-U.S. institution. We've had one or two compliance oversight investigations that involved non-U.S. institutions. In at least one, we contemplated doing site visits but there's an obvious problem in that the site visit would have had to have been organized through the State Department and could only have been done with the permission of the host country. It is my feeling that there are probably not very many host countries that would let in an OPRR investigative site visit team to examine research at their institution. In that particular case, we were successful in being able to interview investigators over the telephone and in person in the United States, and we were able to take some action in terms of corrective actions relative to the research.

But you are quite correct in that we certainly don't have the same oversight authority that we would have to conduct an inspection, for example, in another country.

DR. SHAPIRO: Alex?

PROFESSOR CAPRON: Can you tell us how many requests you have had, if any, for your waiver because of the equivalent provision?

DR. PUGLISI: For equivalent protections? I don't think we have ever had a formal request. Certainly we have never had a request from another country for a determination of equivalent protections. We have occasionally had researchers who have said to us, "These are the protections that are in force in our country, we would like you to accept them, can you accept them?"

Typically what happens is that we very delicately negotiate an assurance that spells out those protections without actually citing the U.S. regulations. In other words, what we have done is negotiate an assurance on a case-by-case basis that incorporated those national protections without a formal declaration of equivalence.

PROFESSOR CAPRON: I'm a little puzzled as to how you would go about negotiating an assurance in situations where you have no first-hand basis for knowing whether what's being represented to you is accurate or, if accurate, is fully revelatory of what's relevant, or where there are local laws or customs that may affect the way the research is conducted. There may be ethnic groups who were the researchers and other ethnic groups who were the subjects. How do you assure yourselves that you're entering into a document that is truly protective of the interests as the regulations require?

DR. PUGLISI: I think the concern that you raise is a valid one. I think it's one that the GAO pointed out even in the domestic context when it evaluated human subject protections; I'm sure you are all familiar with that report. All I can say to you are two things. We have a system of human subject protection in the United States that is essentially based on trust relationships. We trust institutions and researchers to follow the rules and the commitments that they have made to us until we find out that they are not doing so.

Secondly, in terms of international research, in negotiating a single project assurance, we have typically a good deal of contact with the principal investigator. And what our assurance coordinator tries to do through talking with the investigator is to make sure that the investigator understands what his or her obligations for human subject protection are. Now, admittedly, that is partly a subjective process and certainly not a perfect process.

PROFESSOR CAPRON: You made mention of the legally effective or legally authorized requirements under the informed consent that you draw from national law. How do you determine that? Do you have consultation with independent persons knowledgeable about the national law of the countries involved?

DR. PUGLISI: We don't engage in those kinds of discussions. What we do is remind the responsible institution or review board, whether it is one in the United States where there are, for instance, perhaps field researchers going to another country to do research, or whether it's a local IRB in a foreign country, that they are bound by their own legal requirements and they have an obligation to make themselves aware of the legal requirements in their jurisdiction, just as we would do with the domestic institutions where IRBs' determinations vary somewhat according to State law.

PROFESSOR CAPRON: I would gather that if in the United States one of the States were to adopt a statute saying that children could be used for risky, non-beneficial research with the consent of court-appointed guardians, let's say children in foster care could be used in this way, that law would attract a good deal of attention in the United States.

DR. PUGLISI: Certainly.

PROFESSOR CAPRON: And you would be aware of it if California, to pick a random example, had adopted such a statute. How are you aware if—I don't even want to mention another country for fear of offending.

DR. PUGLISI: You're absolutely correct, we're not aware of it.

PROFESSOR CAPRON: And, in effect, such regulations or national laws on who is legally authorized to give consent and what is legally effective consent, are the substance at the heart of what you regard as one of the three primary protections provided by our Federal rule. And if we are dealing with a nation, and I'm not saying we are, I'm just saying we apparently don't know if we are, that varies in that respect, might we then be in a situation where the compliance with our national expectations would be on paper only and, in fact, research could be conducted which would never be allowed domestically even though sponsored by Federal dollars?

DR. PUGLISI: I think there are two considerations. First of all, the regulations do set a minimum standard for what constitutes legally effective informed consent. So there would have to be, for instance, the eight required elements that are specified in the regulations. On the other hand, you're quite correct in pointing out that we have no way of knowing who would be a legally authorized representative for either a child or someone who had diminished capacity to consent.

PROFESSOR CAPRON: Finally, you mentioned this problem that you would face in investigating a complaint. I am slightly puzzled by that and I wonder whether the Department has resisted the notion, or just hasn't yet had the authority, or thinks it doesn't have the statutory basis for the authority, to link with the assurance a requirement that states, in the case of a problem in need of investigation, that by accepting these funds and filling out this assurance, you agree that you will allow inspectors to come and make an onsite inspection or otherwise produce documents for them to answer legitimate concerns about the research?

DR. PUGLISI: Clearly, a commitment has been made through the assurance that the institution would allow appropriate review of documents by OPRR and by the funding agency if there were a problem. They've made that commitment on paper. The reality, however, is that things become infinitely complicated when the constraints of diplomacy become involved. I can only speak from the one circumstance where I've had personal experience. In that particular case, the situation was complicated by the fact that there was no actual HHS support in terms of money provided, but rather an intellectual contribution by HHS employees and HHS materials provided to the researcher.

PROFESSOR CAPRON: I'm not sure that I understand. Are you saying that in a situation in which you actually had funds, part of this $100 million-plus that flows just from NIH, and I gather there's more money from CDC, and so forth, even within HHS, that flows to an international researcher, that if you had the kinds of complaints that we have heard about some domestic research, you would feel that the assurance form would allow you to investigate—and then you would be subject, I understand, to the greater difficulties that you would have to have support perhaps from the State Department or otherwise—but that you would feel you had the agreement that they would allow it? Or is the agreement limited to their providing whatever documents they choose to provide, but not allowing you to do the kind of onsite inspection that you've done domestically when there have been problems?

DR. PUGLISI: We would operate under the assumption that we had the authority to conduct whatever

inspection or investigation we needed to. The first thing we would do would be to try to determine on the basis of the evidence that we had at hand, even if it is limited evidence, whether or not human subjects were at risk. If human subjects were at risk, we would suspend the assurance, which would have the effect of stopping the flow of HHS funds to the institution. That, ultimately, is our greatest weapon, being able to stop those HHS monies.

If we thought human subjects were at risk, we would stop the flow of HHS funds and then we would begin the process of trying to do an investigation. That would include both getting whatever documents we could get from the institution and initiating the process of trying to conduct an onsite review, for which we would have to go through the State Department.

PROFESSOR CAPRON: I gather that in the United States the threat is much greater than it would be, stopping the funds, if the threat could apply to the institution's eligibility. If you have 450 multiple project assurances, only one of which is international, those are the assurances, along with the cooperative ones I suppose, where the threat that funds will be stopped is the greatest. If you have a single project assurance and the funds have been sent, the institution then faces the difficulty of getting another single project assurance.

DR. PUGLISI: That's exactly the case.

PROFESSOR CAPRON: Your leverage is a good deal less. I want to make it clear that I'm asking these questions because one concern of our looking at the international area would be are there adequate means of assuring that when Federal dollars are spent, they are spent in a way which is appropriate? And if the answer is that you don't now have the authority, it's not a matter of criticizing OPRR for what it has done, it may be a matter of saying additional legal authority is needed. My own understanding of your answer is, no, you feel you have the authority to both threaten that funds will be stopped and to stop them if necessary, and to gather whatever information you need by whatever means. There may be logistical difficulties, but you have that authority. You don't feel you need additional statutory or regulatory authority.

DR. PUGLISI: That's correct.

DR. SHAPIRO: Thank you. Arturo?

DR. BRITO: A general question and clarification for the regulations. There are some exceptions to IRB approval within the common rule. How does this apply to international research? In other words, the surveys, et cetera, of general populations and all, how does that apply?

DR. PUGLISI: The exemptions that would apply domestically also apply for international research. Also, an international IRB has exactly the same prerogatives as a domestic IRB would have; for example, to waive the requirement for informed consent under certain circumstances. It works exactly the same way.

DR. SHAPIRO: Alta?

PROFESSOR CHARO: I want to pull it back a little bit to kind of a big picture scale so I understand the range of concerns that are raised here, some of which seem to be uniquely procedural and some seem to be more substantive.

The three areas so far that I have heard that are troublesome are, first, the quality of the independence of the human subjects and their ability to genuinely consent, with subsidiary issues about the evidence of that consent.

The second are the kind of distributive justice questions that were raised by the AZT trials, some of which are not answered by compliance with the regulation because they are about the substantive judgments of the IRBs; that is, risk-benefit analyses, levels of care for the controls, equitable selection of subjects, some of which are addressed by the subparts. But, in general, for those agencies subscribing to the common rule in the U.S. that don't subscribe to the subparts, those are topics that are beyond the purview of our current regs.

And the third being enforcement, which Alex has talked about.

Would you say that there are any other kind of large categories of concern in the conduct of transnational research that don't fall under this?

DR. PUGLISI: I think the biggest concern I have, given that we, as I said before, essentially have a system that is built on trust, is making sure that the investigators really understand their responsibilities for protecting human

subjects. We need to make sure that we do a very, very good job of educating people who collaborate with U.S. researchers in research or receive HHS funds for research.

In the example that I referenced earlier, we had an investigator who had signed a single project assurance and we questioned him directly about his failure to comply with that assurance. He told us very straightforward and candidly, yes, I signed it, I didn't know what it meant, and I didn't really read it very carefully.

So, getting a signature on a piece of paper is all very nice from a legal standpoint. The more important protection I think is making sure that researchers, both international and domestic researchers, really understand what their responsibilities are for protecting human subjects. That's really the big challenge that we face.

PROFESSOR CHARO: May I follow up with just one other question? When you've got an example of collaborative research between a U.S. investigator and a foreign counterpart, such as under the multiple project assurance at my own institution—and I wonder if this is typical—IRB review is going to be required at both our institution, the U.S. institution, and at the foreign institution, as well as where the research is going on or where the collaborating investigator is located.

Just as in multiple IRB reviews within the United States, we have found distinct differences in tolerance for certain kinds of risks as between these different IRBs. And in these cases, it is often strongly influenced by local culture, as well by regard for certain kinds of people. We've seen it particularly with women where there are additional complications on consent. The resolution we've had so far is to simply tell our investigators that they just can't do it unless we agree, period, end of story. And they're not happy with that.

DR. PUGLISI: That's what you've pledged to do, by the way, under your MPA.

PROFESSOR CHARO: I know that's what we've pledged to do and we've been doing it. But I would be interested in knowing about the way other institutions have handled this, or if there is any other way that they've handled it, because this seems to be the classic recurring situation.

DR. PUGLISI: I don't have any data. I can give you impressions. I think there are a fair number of institutions that handle it just the way you have described. I think there are some institutions that are willing to defer to the IRB onsite, or at least to listen very carefully to the point of view of that other IRB. There are probably other institutions where they simply do not require a local review unless there is HHS funding involved.

The ideal situation would be for the two IRBs to communicate with each other and reach an understanding. That's pretty hard to do even domestically. It's much harder to do internationally.

PROFESSOR CHARO: Thank you.

DR. SHAPIRO: Any questions from the members of the Commission? Once again, thank you very much and I hope, Tom, you'll be able to stay a few moments longer till we complete this part of our program.

DR. PUGLISI: Certainly.

DR. SHAPIRO: Next, we're very fortunate to have with us this afternoon Professor Bernard Dickens from the University of Toronto. He will talk to us about international instruments for human subjects protection, with particular emphasis on the characteristics of ethical concerns in research conducted in underdeveloped countries.

Professor Dickens, it's a great pleasure to have you with us today. Thank you very much for coming.

INTERNATIONAL INSTRUMENTS FOR THE PROTECTION OF HUMAN SUBJECTS -

Professor Bernard Dickens, University of Toronto

PROFESSOR DICKENS: Thank you, Mr. Chairman, it's a great pleasure and privilege to be here. I'm afraid I do have to begin with multiple apologies. The first, of course, for being late and causing you to change the sequence in presentations. The second apology is because although most of the documents that I'm going to cite you have already distributed, I do have one or two others that, because of travel, I didn't have the chance to make available in advance. The third apology is that, to an extent, I am going to be a little repetitious in that I will be touching on some of the issues already raised.

The initial point to make about international documentation is that it reflects international sensitivities and these evolve over time. We tend to suppose that we have the appropriate language in which to discuss research, and it's quite common to speak about research involving human subjects. But it could be that although this is a convenient description, that those who take part in research, it may be objectionable. There was a meeting in the Summer of 1996 of a circumpolar research group involving people from Greenland, Siberia, and Canada of the native aboriginal populations and they took very strong exception to being described as "subjects of research." They pointed out that subjects are persons under the control or authority of others and, while in the past they recognized that they had, indeed, been subjected to procedures, they felt that their autonomy and dignity required that they not be described in this subjective state. The contrast was drawn between autonomous sovereigns and those who were subject to sovereigns. And they demanded that the word "subject" not be used and, in fact, the description of "participant" was more agreeable to them, though this raises ambiguities, of course, because investigators are also participants in studies.

The instruments that I'm going to refer to are essentially the ones that you have, in particular from the Council of International Organizations of Medical Sciences (CIOMS). Professor Capron has been very much involved in the activities of CIOMS, on steering committees of one of the conferences and consultant to the other. And, in a sense, I'm certainly not telling him anything that he doesn't already know.

The relevance of CIOMS, which is set up jointly by the World Health Organization and UNESCO, though it functions essentially from the World Health Organization based in Geneva, is that it attempts to mediate between investigators from developed economies and those from industrially developing countries. In addition, we have heard that the Council of Europe are dealing essentially with industrially developed countries. There has been activity in the field of regulation of a number of biomedical activities in which research is prominent. And this range does give us a need to pay attention to the way the United States is perceived. Somewhere in between we have the British Commonwealth Medical Association, which deals with both developed and developing environments, though in the context of research, in order not to reinvent already well-rolling wheels, the Commonwealth Medical Association hasn't taken special initiatives—it simply requires that existing guidelines be observed.

An important difference though is that a number of industrially developing countries look to the United States for technological and economic advance and leadership. But in many developed countries, there is a sense that the United States social justice, in equity and access to health services, is less advanced, and this creates a somewhat different environment, a different background against which health preserving and promoting interventions can be assessed.

The Nuremberg Code is perhaps the benchmark that we ought to take. The code itself, you realize, was essentially based on U.S. practice. The Nuremberg War Crimes Tribunal conducted proceedings against the major war criminals, but the trial of the so-called Nazi doctors was conducted under United States auspices; the judges, the council, the expert witnesses came from the United States. Nevertheless, the Nuremberg Code, interestingly called a code, bringing in together what already exists and making it obligatory, has been widely accepted internationally as setting a benchmark.

There's a certain analogy, I think, to the Hippocratic Oath; that is, the phrases used with reverence and deference. But the code is more frequently cited than actually read. And when one reads it, one finds surprises in the Hippocratic Oath because of what it includes, and in the Nuremberg Code because of what it excludes. It serves a useful function, though. It gives us some measurement of how far we have evolved and, in that sense, it gives a focal point on what has changed. The Hippocratic spirit dominates the practice of clinical medicine. The spirit of the Nuremberg Code, evolving from the cynical exploitation of vulnerability where individuals were literally tested to destruction, gives us a benchmark to measure from.

But if you actually look at the Nuremberg Code, and reference has already been made to this, because of its rigid insistence that those who are participants in studies give their free and adequately informed consent to it, it follows that those incapable of informed consent cannot be participants in research. This, of course, would exclude the whole field of pediatric research. It would exclude the field of research in many affected with mental health conditions and those suffering traumatic head injuries.

In addition, of course, there's no reference to confidentiality in the sense that those who were subject to the experimentation that Nuremberg focused on might have regarded confidentiality as the least of the interests they had to

lose. But this is something that today we regard as very significant.

The Nuremberg Code also focuses on biomedical experimentation. And, of course, today we recognize that there are other disciplines that can contribute to our understanding of health care. The social sciences, the natural sciences, psychology, for example, are now regarded as very important in developing research into clinical medicine and obviously into health system research.

The origins of the Nuremberg Code, again very specific to time and place and circumstance, couldn't contemplate ethical duties of equitable inclusion in research of those who could benefit from the outcome. The inclusion of women is something of importance, the inclusion of minorities, the inclusion of low-income people, and of elderly people, these are all matters that today you would regard as critical to social justice and the access that is guaranteed by international instruments to the benefits of scientific progress. So today we recognize that there are ethical duties not only not to undertake violations of the physical integrity of nonconsensual, vulnerable people, there are also duties to include research on those who want it because of the benefits they believe it to promise. And clearly, because of the origins in the Nuremberg Code, there was no reference to including people in studies.

In addition, and this is perhaps one of the major points I want to make, the focus of Nuremberg was essentially what today we might call micro-ethical. It was concerned with the protection of individuals. But public health studies and epidemiological studies, are currently recognized to be very important to health care. Of course, one is frequently confronted with the recognition that many of the contributing factors to the health stages we enjoy have not come through pioneering work in drugs or surgery, but through public health innovations—the control of polluted water supplies, the quality of the air that we breath, environmental ecological factors. And, of course, none of this is reflected in the Nuremberg Code.

The Declaration of Helsinki, promulgated by the World Medical Association, is frequently taken as one of the more significant modern variants of the Nuremberg Code. This has been successively revised in 1975, 1983, 1989, most recently in 1996, and I'll be commenting shortly that the American Medical Association took initiatives to have a further revision at a meeting in November of last year. Because of the relatively short notice at which I came to this meeting, I haven't been able to see what came out of the November 1997 meeting of the World Medical Association.

An interesting feature of the World Medical Association's declaration is its modesty. It begins as recommendations guiding physicians—recommendations that guide, not govern. It goes on to observe that—I'm quoting now from the final paragraph of the introduction—" because it is essential that the results of laboratory experiments be applied to human beings to further scientific knowledge and to help suffering humanity, the World Medical Association has prepared the following recommendations as a guide to every physician in biomedical research involving human subjects. They should be kept under review in the future. It must be stressed that this plan as drafted are only a guide to physicians all over the world." Its final sentence is, "physicians are not relieved from criminal, civil, and ethical responsibilities under the laws of their own countries."

This is a matter that warrants some degree of attention because I gather that in the United States conformity with Federal regulations will make legal what otherwise might be illegal. In other countries, including my own, conformity to ethical guidelines does not give any absolution from ordinary liability under common law or statute. We have a major problem, and I think it is shared in other countries, with regard to pediatric research on newborns, children, and infants, in that it's not clear that parents have general legal authority to dedicate their children to medical interventions other than for the benefit of those very children; not for the benefit of the community at large. And it's not clear that conforming even to the fastidious standards of the U.S. federal regulations would give any protection to a parent or a research institution before a Canadian court and this is something that we struggle with.

Another basic principle of the Declaration of Helsinki has come under some degree of challenge, and, indeed, one of the proposals of the American Medical Association for reform focused on this particular provision. It comes in the fifth of the basic principles, and perhaps I could read that to you. "Every biomedical research project involving human subjects should be proceeded by careful assessment of predictable risks in comparison with foreseeable benefits to the subject or to others. Concern for the interests of the subject must always prevail over the interests of science and society."

Now this is a noble principle and, of course, we can see its origins in the Nuremberg Code. But it presents problems that perhaps we can conceptualize by thinking of the testing of a new drug—let's call it Thalidomide Mark II.

Now if there is a risk to the unborn from the use of the product, one could understand the exclusion of women of reproductive age. One might want to go further and try to estimate the actual risks of the woman being pregnant, but this can involve very indelicate questioning of lifestyle and it could be, in a number of circumstances one might think of, that it is better not undertaken on grounds of ethics and, perhaps more historically, even gallantry.

The difficulty, of course, is that if the product indeed is like Thalidomide Mark I but it is not tested on women of reproductive age, then its devastating effects on the unborn won't become apparent until perhaps after a decade of "therapeutic" use undertaken in good faith by both prescribing physicians and consumers, and epidemiologists may eventually be able to measure the nature and extent of the devastation caused by the drug.

Now, the American Medical Association has recommended that there be an addition to this provision. It has recommended that the same phrase be used, the interest of the subject prevailing over the interests of science and society, but it then has proposed this addition: "Subjects may, however, elect to participate in research that they are aware will have no direct benefit to themselves if the protocol has been approved by an independent research ethics committee and the anticipated benefits of the knowledge to be gained are proportionate to the known and anticipated risks." In this circumstance, fully informed prospective research subjects may voluntarily and altruistically consent to accept discomfort or inconvenience in order to advance societal and/or scientific interests knowing that there will be no personal health benefit.

Now this, of course, may open the way to the inclusion of women of reproductive age and circumstance in studies that could be harmful to the unborn child. But, of course, even this language only permits the participants themselves to waive their own protective interests. This leaves the ethical question of the extent to which women can jeopardize the interests of unborn children and the extent to which investigators can ask them to do that.

The Helsinki Declaration also draws a distinction, that is on the verge of being abandoned, between clinical research, described as medical research combined with professional care, and nonclinical biomedical research, that is nontherapeutic biomedical research. A leading U.S. authority, Dr. Robert Levine from Yale, has been very critical of this distinction, saying that it is a false distinction and sort of confusion and danger. And the American Medical Association proposal is that this distinction be abandoned and that the different elements in the study be addressed as such.

Let me come to the CIOMS guidelines, that is the 1991 guidelines on epidemiological studies, and the 1993 redrawing of guidelines initially promulgated in 1982. The first, the international guidelines for ethical review of epidemiological studies, and the second, international ethical guidelines of biomedical research involving human subjects. The latter of these, the more recent, in the sense is more traditional. Clearly, it is the epidemiological guidelines that I think warrant particular attention because they do address the need for public health research.

The 1991 guidelines were really driven by the WHO component of CIOMS and, in particular, the global program on AIDS. This was confronting problems in HIV/AIDS research, particularly in developing countries, not limited to East Africa though East Africa was a focal point of major concern, and many of the examples in the 1991 guidelines are drawn quite deliberately from the HIV/AIDS area of research. Today, perhaps we could project this on to the issue of research in developing an HIV/AIDS vaccine. The principles, of course, are applicable to other medical technologies—new reproductive technologies, organ and tissue transplantation—and they really draw attention to some of the cultural shifts between industrially developed countries and those that may have a very profound culture but which are not industrially developed.

One of the issues that has been addressed and it has many ramifications is the appropriate role for commerce and the extent to which individuals can seek to profit in material ways from their own availability and the availability of their body tissues for purposes of research. In the context of organ transplantation, for example, some cultures based on social reciprocity would see a so-called rewarded gifting as simply being culturally proper, whereas in industrially economically developed countries, we tend to regard the exchange of body tissues for money as being of essentially commercial character. So there can be cultural difficulties.

In view of the time, I won't elaborate on this. But I will draw attention to the fact that in the United Kingdom, which today, of course, is culturally pluralistic and has gone far beyond its historical Anglo-Saxon origins, the Human Fertilization and Embryology Authority last month in February issued a consultation paper on the implementation of withdrawal of payments to donors of gametes, and this could be applied to pre-embryos as well. This gives some

intimation of how immediate this issue is of seeing the proper accommodation and the proper prohibition perhaps of commerce in making materials available, in this context, of course, for the birth of children, but it has an application to research as well.

Let me come to the field of public health studies. These are different from clinical studies in a number of material ways. The first is that individual consent may not be relevant; indeed, it may not be obtainable if one is dealing with a population group. If one is dealing with access to even individually identifiable medical records, it may not be economically or practically feasible to trace the individuals and ask for their informed and free consent. That is, consent may have to be given at a collective, at a political, at a social level. And in some countries, including my own, in my own province of Ontario we have legislation setting up a mandatory cancer registry in which those diagnosed with cancer will have quite intimate details recorded and the recorded data will be available without their knowledge and consent to cancer investigators. This is because of the political assessment that the public interest in gathering information and having superior interventions in the context of cancer justifies this invasion of ordinary principles that at the clinical level we think ought to predominate.

The 1991 CIOMS guidelines deal with community agreement, sometimes called authorization, and this is something that could transcend individual consent. This leaves the ethical challenge of how one accommodates individual dissent; that is, if individuals want to be excluded from the study, there are practical and ethical questions about how one responds to that. Of course, one crude response is to say it can't be accommodated because it would damage the epidemiological interpretation of data. And if resources are going to be allocated with some precision, then one needs accurate figures and one can't let individuals exclude themselves if they want to. Of course, there are lesser harsh responses that may also be proper within limits.

The guidelines also address different sorts of collectivities, that is those that exist independently of any intent to study them, that have perhaps their own social, political leadership where individuals in democratic authority within those institutions can claim in some legitimate way to speak on behalf of all of their members, not to compel individuals to submit to what those individuals may find objectionable, but to say that they can be approached and their individual judgment can properly be taken. In contrast, of course, we have groups that are simply the construct of investigators. That is, if one proposes to do studies on the individuals within a given age range, 18 to 38, who are 25 percent above average weight, one can create that group as a statistical construct. But, clearly, you can't speak to any member of that group as a representative of any others. So just what is a group, what is a collectivity becomes a matter of importance.

We get some sense of this by considering studies that have been proposed quite recently into detection of the gene associated with breast cancer. We've had objections, in particular, by Ashkenazi Jewish women that even if individual participants give their free and informed consent, this research could be harmful to the group as such because those identified with that group could be prejudiced in obtaining health insurance, disability insurance, and life insurance. And so although each individual may find this agreeable, it could be that the collectivity is harmed by this sort of research. And how this weighs in the ethical balance is a matter of concern.

The 1991 guidelines also deal with research in the discipline of the social and psychological sciences, including incomplete disclosure and sometimes incorrect disclosure, deception, which could be necessary in certain methodologies. The so-called Hawthorne effect is that individuals, as a courtesy and a social lubricant, are inclined to do what they think others expect of them. And if they believe that investigators are looking for something, they may be disposed to make it available to them in terms of their responses or behaviors. That, of course, confounds the whole nature of the study. So it could be that one can't state what the purpose of the study is. One may have to misstate what the purpose of the study is.

There are rules governing this of debriefing individuals, perhaps even letting them withdraw data that have been obtained this way. One also has the rule that nothing can be withheld that might induce people not to take part in the study. In that sense, there can be no deception about the nature of the risk; there can be deception about the object of the study. And the 1991 CIOMS guidelines attempt to deal with this.

Other issues affect the acceptance. There can't be coercion, there can't be duress, but there can be problems of undue inducement. That is, if one is dealing with people who are in underdeveloped communities, deprived communities, then they may easily be induced to take part in studies. And, of course, an international aspect of this is that if, for example, a drug company from a developed country proposes research in a developing country, then it could

that a benefit to the participants in the country itself is that there will be access to superior health services to those ordinarily available. Is that an undue inducement? One accepts that there can be obligations to train local people so that something of value is left in the country, and objection has been taken to the so-called bleed-and-fly research projects in which investigators from developed countries move into a developing country, take their body samples, get their data, fly out and leave nothing of any advantage. But what is proper inducement, what is undue inducement is a matter of some difficulty.

The final point I'll make is the one already addressed, that is the need to make relevant assessments of what is culturally appropriate. Not every community even within North America gives the recognition to autonomy that has become very fashionable in modern practice and rhetoric. Again, what is to be protected under rules of confidentiality could be a matter on which views differ. Some individuals could be hypersensitive to an ordinary way of looking at things, or they may well have no inhibition about their disease state or the genetic characteristics of their family being publicized. Family structures and family functioning could well differ, and we've heard that assessments of risk could differ.

So the different guidelines that we have do try to sensitize investigators and provide some modus operandi under which research can be conducted of a transnational character in which there are cultural incompatibilities that have to be overcome between investigators, sponsors of studies, including international agencies, and the inhabitants of countries and regions within which research is conducted. Perhaps a true final word is that if we take attention to underdeveloped communities, we can find those even in the centers of our own vast cities.

DISCUSSION OF INTERNATIONAL RESEARCH ISSUES - Dr. Harold T. Shapiro and Commissioners

DR. SHAPIRO: Thank you very much. A number of Commissioners would like to ask some questions. Larry?

DR. MIIKE: I was interested in your brief discussion about the difference in clinical and public health research. Is the issue with the public health research where you can override the privacy rights of the individual the characterization of the potential harm that occurs in clinical versus public health research?

PROFESSOR DICKENS: Yes. But this turns on the distinction that is sometimes drawn between privacy and confidentiality. Privacy is taken to be the power to control what others know, and we all give that up. On every occasion when we appear in public, people can look at us and draw implications about our health, even our lifestyle. The issue, of course, in medicine is that one gives more to physicians and those who offer health services than one might be willing to give even to close members of one's family. And sometimes health professionals can infer from what is presented more than the patient realizes that he or she is disclosing.

DR. MIIKE: I guess the issue for me is as an individual, and maybe I'm mis-characterizing it, there's a collective judgment that I can make a decision to participate in something that might be physically dangerous but nobody gives a damn if I get totally offended by their using information on me without my permission.

PROFESSOR DICKENS: Yes. And this has to be put into the wider context of the public interest. This Latin text —

DR. MIIKE: Yes, but one can make the argument that clinical research is for the public good, so I can interchange clinical research with public health, and I would come out topsy-turvy. You can think that clinical research trials for therapeutic reasons are as much a public health benefit for the population as your classical epidemiological-type studies. It begins to become a matter of semantics to me.

PROFESSOR DICKENS: Yes.

DR. MIIKE: The reason I raise this is that I think where we're heading in our biological materials side is that if there is harm or an invasion of privacy on the individual then we need consent, and you can't just impose studies on them. So I'm not sure we're making a distinction between clinical research and public health research in our human biological studies.

PROFESSOR DICKENS: The distinction often drawn is that there is no justification in public health terms for undertaking physical invasions. Though, of course, we have seen compulsive vaccination programs and that, obviously, is physically invasive. That is justified in terms of the public interest.

Normally, one supposes that public health studies would essentially be data-driven epidemiological studies, and information would be taken, even identifiable information, from individuals whose individual veto may not be accommodated. That is, the decision to conduct the study is a public/political decision.

DR. MIIKE: But that's exactly the point I was trying to make. That in public health initiatives, in the old days you could have been in prison, a TB patient, so there times when there are physical harms to people in public health initiatives for the public good, but it's a physical harm against the individual. So I'm having even greater trouble in those instances distinguishing that from the clinical research situation.

PROFESSOR DICKENS: Yes. The difference, of course, is obscured in the emphasis we give to the phrase "public health." We emphasize the health component. But, in fact, I believe the U.S. constitutional law and in the laws of other countries, the public health power is derived from the policing power of government. It includes the power to detain people who have not committed any offense, that's quarantine, it includes the power to treat people over their preferences, it includes the power to force them to give information for contact-raising. The Public Health Service is a uniformed service represented by the leaders in the field. The Surgeon General appearing in uniform in public is making the point that this is a public service. And perhaps if one emphasizes the "public" rather than the "health," you get some sense of this.

DR. SHAPIRO: Alta?

PROFESSOR CHARO: First, Bernard, you can be gallant for me anytime. I kind of miss those days.

I feel like in the discussion in the CIOMS document that there are two themes that are in conflict with one another, and I just want to understand which way they're being resolved. On the one hand, the question of inclusion has been addressed as part of the new paradigm of research and implicit in here is the notion that inclusion is not something limited simply to women or to racial and ethnic minorities within a particular country, but that really research on a global scale with globally representative populations is necessary if you're doing basic health studies and you want to understand how things operate against a backdrop of nutritional patterns, other kinds of lifestyle patterns, etc. Which would argue for the fullest possible inclusion of people from all economic walks of life and from all levels of development in their home countries.

At the same time, there is in many of the guidelines that come down the pike, starting from I think around seven, a lot of attention to the specific problems that take place when you're doing transnational research in developing countries where there is not as well developed a research ethic, where there might be stratifications in society that are quite extreme on a broad scale and that invite exploitation as a pattern, or diminish the capacity for genuine independence and consent, which would seem to argue for avoiding those settings until one has an identifiable need to operate in those settings. Isolating your research as much as possible in the more educated, developed country settings, even within the developed countries in the more educated populations in order to maximize your chance of genuine independence, particularly when it comes to altruistically opening yourself up to taking on risks for the benefit of general knowledge.

The two tendencies seem to be conflicting. I couldn't quite sense in this document, even in the most general way, which way you're trying to see international research jump on this question.

PROFESSOR DICKENS: I think in part you addressed this in an earlier question when you mentioned the need for ethical review both in the sponsoring country and in the host country. The supposition is that the host country reviewers would have a sense of local needs, local priorities, what values can be sacrificed in promotion of which others. The functional problem, of course, is that frequently those who claim to speak on behalf of their countries have no democratic credentials and have no democratic answerability. And in that sense, one has to guarded about what sort of initiatives one takes.

It is hard, and one can't really answer it in any adequate way in the abstract except in the rather cynical comment sometimes made about the ethic of inadequate resources—that if something is really worth doing, it's worth doing badly. That is, if the alternative to doing it badly is not to do it at all, then do it as best you can. A number of studies I'm afraid are undertaken on that basis. One hopes for better. But if the ideal is the enemy of the adequate, then you have to do the adequate.

DR. MURRAY: Professor Dickens, as you're well aware, one of the issues around international research

which has gripped the American public at least in the past year or so has been the issue of the use of placebo groups in less developed nations when there are standard treatments available in nations which can afford them. I wondered if any of the documents that you spoke about today offer a specific guidance as to how to respond to those kinds of concerns?

PROFESSOR DICKENS: Not very specific. The Helsinki Declaration as amended does address the need for individuals who are involved in studies—sick individuals in need of care—to be measured against the best standard available; that is, not against a placebo. But this raises the questions that you're well aware of—of how effective the standard treatment is. The issue remains contentious, though the general momentum I think, is against having the placebo controlled studies when there are therapies that are available—not just in a clinical sense—but in a functional economic sense.

DR. MURRAY: I'm sure you're aware that in some of the cases that have been brought to public attention, we don't make judgments about particular cases on this Commission but we use them to raise general issues

The claims at least from some of the local defenders of these studies had a couple of components. One of which was, this is a treatment that simply because of the lack of infrastructure, that is a standard accepted treatment in developed countries, it simply is we can't do it here. Even if we had the money, we can't do it here because we lack either the health infrastructure, refrigeration, follow-up, etc. We can't do it, number one.

And two, even if we could do it, we couldn't afford to do it. And there is a plausible case to be made that a less expensive, less onerous form of treatment or prevention might actually be as, or almost as effective, and we would like to test that.

That's the kind of defense that has been offered. I just wondered, again, if you have any comment about that?

PROFESSOR DICKENS: None of the international documents that I'm aware of deals with the issue at that level of sophistication or specificity. Sometimes the guidelines are inverted, in that although they say that there should be access to the best possible standard care, the inversion comes in the interpretation that this means individuals should not be deprived of what they would otherwise enjoy. If, of course, they wouldn't enjoy anything, then there's nothing really to deprive them of and you may, therefore, say that provides a justification for a placebo-controlled study.

DR. SHAPIRO: Thank you. Alex, then Eric, then Bernie.

PROFESSOR CAPRON: I guess I'd like to follow up on that. You may not have been here when Duane Alexander quoted Pavl Riis of Denmark, one of the drafters of the original Declaration of Helsinki, who gave us a drafter's gloss on the phrase which he thought was self-evident, the one to which Tom Murray just alluded and which you cited, which is Section II.2 in the Helsinki document. I'm tempted to put you in the role not of James Madison but of John Marshall, to use an extension of our Constitution, since you are so widely regarded as an authoritative interpreter of these documents.

The gloss that was cited was the notion that it was understood that the best current method available in local practice was part of the unspoken phrase. Do you know of other situations where international bodies or other commentators have addressed this issue prior to the current concern over the AIDS research where we might get some sense if we try to reach conclusions about the most sensible way to interpret guidance of this sort?

PROFESSOR DICKENS: The short answer to a sophisticated question is, no. I'm not aware of any more profound addressing of this issue than Dr.Riis has given.

PROFESSOR CAPRON: I wanted to ask you to clarify two points very quickly that came up in passing. One was this mention of the notion of incomplete disclosure of the objectives of research to subjects under the heading of the epidemiological studies. It is true in that circumstance, however, that the IRB has to be fully informed and has to be agreeable. Is that the—

PROFESSOR DICKENS: Yes, yes, absolutely.

PROFESSOR CAPRON: And that where the emphasis is on study of a community it is the expectation that there will be representatives of the community on that IRB, really representatives of the community in a way in which just being a member of the community isn't as representative, as I understand it. The sense is somebody who can really speak for the community; is that—

PROFESSOR DICKENS: Yes. The CIOMS guidelines do require that membership of the committee include those from the community to be studied. But the question of how representative that person is - is really a political question.

PROFESSOR CAPRON: Another point you mentioned was situations in which the community could assent to research which is then not carried out with individual consent. And I think you and Dr. Miike had an exchange then about what public authorization lies behind such a public health study. There is also reference to community agreement where the interests of the community might be harmed by the findings of research. That's suggested in, the other was one was I think Section 5 and Section 39 there's some suggestion there. Is it your reading of that if a researcher had willing subjects but the representatives of the community were unhappy with the research going forward, and you mentioned, for example, Ashkenazi Jewish women in the cancer studies, that under a correct reading of the CIOMS guidelines that research ought not to go forward?

PROFESSOR DICKENS: No. The guidelines I think address the process of decisionmaking rather than what the decision itself should be. The research is not prohibited under the guidelines. But any committee willing to approve research over the known opposition of those claiming to speak for the community would have to give an account of why they felt that was ethically appropriate.

PROFESSOR CAPRON: And then if I could ask a question to you and also get a response from our HHS representatives. You mentioned two things which it seems to me are very important for our understanding. The first is the effect for a researcher of following research regulations where the activity is said on other grounds to have violated the positive law of the jurisdiction. I understood you to suggest that in most of the world following the research guidelines wouldn't do you any good but your understanding was that in the United States it would. I'm not aware of that as a reading of the U.S. regulations. That is to say, I took the regulations to say this is what you must do to get Federal funds but if, in the process, you've actually departed from some law of the jurisdiction and committed harm to someone, you are still liable and this is no defense. Your reading was somewhat different, unless I misunderstood you.

PROFESSOR DICKENS: No. It wasn't a reading, it was an attempt to summarize what I've heard. Clearly, I defer to your interpretation of the status of the Federal regulations in U.S. law at both Federal and State levels. It was my understanding that because of the legislative foundation of the Federal regulations conformity with them meant that research that was in compliance was lawful research.

PROFESSOR CAPRON: Maybe we could get then an answer from the U.S. side from Dr. Puglisi?

DR. PUGLISI: The HHS regulations and the Federal policy include the specific statement that the regulations do not preclude any State or local law that provides more stringent protections for human subjects. So conformity to the HHS regulations or the Federal policy does not make something okay if it's not permitted under state law.

The only qualification I can make would be that in some States, specifically California where there are specific statutes that relate to human subject protections, there's a provision that research that is conducted in accordance with an HHS assurance may follow the Federal regulations rather than the State regulations.

PROFESSOR CAPRON: But I gather that is just a reference to whether in areas where there wouldn't be Federal jurisdiction the State expects the researcher to follow the U.S. rules anyway. But that none of this is a waiver of tort law standards if there was a finding that despite whatever regulatory things you've gone through there really wasn't adequate consent, etc.?

DR. PUGLISI: That's correct.

PROFESSOR CAPRON: And the final question, also for both of you, is, it seems to me that the Helsinki Declaration's division of the beneficial-nonbeneficial or therapeutic-nontherapeutic or clinical-nonclinical, which is the actual language it uses, is not reflected in U.S. rules. I want to know, do you agree that there is that difference? And then from the U.S. side, I wonder, if that is the case, then how is it that we can accept an institution abroad saying that it will comply with the Declaration of Helsinki as an equivalent of following our rules since the Declaration of Helsinki seems to me to give a broader sweep to the so-called clinical research and is, indeed, I think historically as a document, understood as a reaction to the Nuremberg Code for the very reasons that Bernard Dickens said. The Code was drafted by American judges passing judgment on people who had used subjects who were clearly non-volunteers in a prison situation for research that was not for their clinical benefit. And, yet, the research community, the World Medical

Association, realized there was going to be a lot of research which couldn't be carried on if you sort of took Nuremberg to be the full statement, and they created a document which had this other, and indeed, predominant role for clinical research with much wider judgment, and it's been toned down in subsequent years, but in the original declaration much wider scope for the judgment of the researcher.

I wonder whether, (a) you agree that there is that difference between the U.S. rules and the Declaration of Helsinki; and (b) from the U.S. side, I wonder how is it then that we can allow the Declaration to stand instead of the U.S. rules when there is this at least tension in the way that they regard so-called clinical research, which Belmont and the National Commission's work seem to say we shouldn't make that divide; therapeutic-nontherapeutic wasn't a good divide to make.

PROFESSOR DICKENS: Clearly, I can't comment on the U.S. position. But I think it is increasingly recognized, not just in the American Medical Association, that the contrast drawn between clinical research-nonclinical research in the most recent variant of the Helsinki Declaration is inadequate. The 1993 CIOMS guidelines say that the Helsinki distinction does not provide for controlled clinical trials and, equally, Phase III vaccine trials would not be accommodated. So I think it's clear that this is a fragile distinction.

Again, I would go back to the introductory language of Helsinki. It is a recommendation, it is a guide and justifiable departures from it I think would be perfectly proper.

DR. PUGLISI: An assurance contains two parts. The first part is a general statement of principles that applies to all research regardless of funding. The second part applies specifically to HHS-supported research. So the reference to an ethical code such as the Declaration of Helsinki, or anything other than the Belmont report, is in reference to research that is non-HHS-supported.

For the research that is HHS-supported, we have the second part of the assurance which outlines the specific protections that are to be enforced, and then secondly, in the case of a single project assurance, we have the particular project being reviewed and the consent document being reviewed by OPRR. In the case of the cooperative project assurances, we have the project and the consent document being reviewed by the funding agency. For a multiple project assurance, I don't think we could accept an assurance that didn't reference U.S. regulations.

DR. SHAPIRO: We have three more people and then we're going to have to take a break because we're running a little late in our schedule.

Eric, then Bernie, then Alta.

DR. CASSELL: My comment may be muddled because my head's muddled about this. Assurances and codes abound, as Professor Dickens points out, but when you get to particular cases, as Tom Murray brings up, they're not much help. I'm trying to go back to the issues that followed the Second World War when the United States was bringing medical care into other cultures, and people were outraged if anybody locally died when there was so much food here and so forth. So we exported dried milk to places where a lactase deficiency was so common that we exported diarrhea. We made mistake after mistake because of lack of knowledge of what could happen in another culture. And that kind of thing at the time was called "cultural imperialism." And we finally learned and all of that sort of stuff.

And then I have this quality of an "ethical imperialism" now. We know exactly what's the right thing to do. On the other hand, in our own country we have seen in the war on poverty the creation of medical services which were then withdrawn the minute the money ran out, causing great harm. And once again, if we did what people wanted us to do and there's no placebo group, we would do the same thing—the study would leave and when the study left so would the medications leave, and we would leave a culture no more able to deal with the disease that they actually have. And I don't have trouble with that.

I have trouble with how we make it clear, not just to investigators but to the public that watches. After all, the outcry didn't come from a bunch of investigators, the outcry came from editors of medical journals, and that certainly must be a pristine place to live, and the citizenry. So I think one of the things we have to come out with is not another code, there are really a lot of codes, but some way to think our way through it and to make that thinking clear to other people.

DR. SHAPIRO: Thank you.

Bernie?

DR. LO: I wanted to ask Professor Dickens to offer his suggestions as to what role NBAC might fill in this debate on international research. And I want to sort of break that into two parts. You very nicely took us through the major codes. I guess one question is, is there a pressing need to try and revise some of these codes in the sense that they really are thwarting important research? And then the second part of the question is, putting aside the codes for a minute, are there issues other than the ones you've raised in your discussion that are extremely important for international research that need more attention and more clarification?

PROFESSOR DICKENS: First on the question of codes, the Nuremberg Code of 1947 is relatively unsophisticated in contrast to the German Medical Code of the early 1930s. This perhaps makes us a little guarded about how valuable it is to have codes. If one sees the spirit with which codes are observed, perhaps one gets closer to their relevance.

With regard to other issues, perhaps I could just mention one. We've seen the United Nations Human Rights Commission and the monitoring agency under the Convention on the Elimination of all forms of Discrimination Against Women (CEDAW), in concluding observations on nationally submitted reports, being very critical of countries that have an unduly high rate of maternal mortality and morbidity associated with the nature of their abortion laws and the operation of their abortion laws, that some have purely repressive laws, other have laws that are more accommodating but don't support those laws with any services.

Perhaps instead of answering the question, I could ask if this is something that you think it appropriate for you to address.

DR. LO: Thank you.

PROFESSOR DICKENS: Perhaps I could add that both the U.N.-Cairo Conference of 1995 and the U.N. Conference on the Status of Women, the Cairo Conference was on population development, the conference of 1996 in Beijing on women's interests, both targeted the problem of unsafe abortion as a public health problem in many countries of the world and not simply a clinical issue.

DR. SHAPIRO: Thank you very much. Alta?

PROFESSOR CHARO: I'd be interested in some clarification on one of the answers that you gave to a question from Alex. He was asking about the community consultation that can take place so that research that might reflect upon a community, he mentioned Ashkenazi Jews as an example, would be open to discussion by community representatives. And you had suggested that if an IRB were to approve such a protocol over the objection of community representatives, they would do it subject to being accountable for having overridden those objections.

What I wasn't clear about is accountable to whom? Since IRB deliberations are confidential, and, at least in the United States, in most cases what you've approved never gets funded anyway so there's never an actual study that goes on that can be the trigger for public discussion, what is the accountability mechanism that you had in mind?

PROFESSOR DICKENS: It's really in a political setting. If research was approved that representatives of the affected community objected to, or if components that they required were not included, then the investigators and the sponsors of the study would have to give some political account perhaps in public health terms of why they thought it proper to undertake research and risk imposing it.

PROFESSOR CHARO: But that's assuming though that you're bringing in outside people. If you have those community representatives on your IRB, they are not allowed to speak outside about what went on in the IRB, at least in the U.S.

PROFESSOR DICKENS: No, but they would be free to engage in public comment, not necessarily saying that their objections were discounted, but saying as members of their community that they find this objectionable because of what it includes or because of what it excludes.

PROFESSOR CHARO: Okay.

DR. SHAPIRO: Thank you very much.

I really want to thank today's speakers for taking their time to come down and share their expertise with us. It's been very valuable to us.

This word to the Commission. I would like each member of the Commission to think some over this afternoon and this evening about our own agenda in this area. I would like to take a few minutes tomorrow perhaps at the very beginning of the morning session, maybe 20-25 minutes, to really get suggestions from Commission members as to how we should focus the scope of our own work in this area.

I've asked Alex to help mobilize those of us really interested in this area to focus the Commission's efforts as we have done in other cases. Those of you who are especially interested in working in this area, please let me know because I'm sure Alex would welcome your assistance. So you might just think about whether that's one of our projects which you are especially interested in. I think there are a lot of fascinating issues here.

But also, more importantly perhaps, to begin a more focused discussion on just what our agenda might be, just which aspects of this fascinating yet multifaceted problem you think is useful for us to take up. I would like to at least begin that discussion first thing tomorrow morning.

Once again, we thank our guests for coming.

DISCUSSION OF HUMAN BIOLOGICAL MATERIALS REPORT -

Dr. Thomas Murray, Dr. Kathi Hanna, and Commissioners

DR. SHAPIRO: I'd like to get our meeting back together. We are running a little bit behind time, but it was well worth it because of the discussion with our guests.

The next item on our agenda is to continue our discussion regarding the use of human biological materials, the report that we're in the process of creating in that area. We have done a lot of hard work on that issue in the last two meetings as we've talked back and forth on just how we're going to approach this issue and what kind of structure we should give our reports. We will have some guests to address us on some aspects of this issue tomorrow as part of our discussion in the morning. That's on your agenda. And while we had some discussions in Los Angeles on this issue and some very helpful discussions, there were aspects of this that we didn't fully consider at that time we need to make sure that we address as we go ahead today.

Let me begin our discussion by just turning to Kathi, who has prepared some materials for us. I think, Kathi, you want to go through at least one aspect of that to begin with and get reaction from Commissioners on that issue. Let me turn to Kathi Hanna.

DR. HANNA: I first want to go over what I think in the next day and a half will be helpful to me at least to proceed to put a report together by the May meeting. So I'll go down the list first and then I'll ask if we can concentrate on one thing this afternoon.

The first is, and this is what I'm going to ask if we can get started on this afternoon, the definitions that are at the very conclusion of the document following the reconfigured boxes. If we can decide or agree on what the different terminology is and what we mean when we are using these different categories, if I understand that we are in agreement on those terms, then that will make it much easier to put the whole document together. So I'd like to get started on that this afternoon.

And if we can get to some agreement on these definitions, then we can turn to the boxes. I've tried to reconfigure the table slightly. So we can talk about that and whether that's useful or not. And I've also tried to indicate where I think we have completed a box and where we still need to talk about what the recommendations are going to be. So that's task two.

I think if we can start on completing those boxes and, therefore, recommendations for prospective collection of biological materials and we can reach some agreement on that, then it would be fairly easy to turn to previously collected samples and make sure that everyone is in agreement on what has been concluded in those areas.

I think it would be helpful also tomorrow to have a discussion about risks and what people perceive as risks so

I have a good understanding of when we talk about things like minimal risk, or risk to the individual, or risk to groups, that we all understand what we mean by that. I think if you're going to try and include some guidance to institutional review boards, then we need to be very clear about what we think risks are.

We still have to grapple with the issue of community. I've left it out of this table for now because I think what I was hearing was that any time that community was implicated a whole different set of considerations kicked in regardless of whether it was previously collected, prospectively collected, in a clinical setting, research setting, whatever. So I think we need to talk about that. We need to talk about how one identifies community, and what we want to tell IRBs or investigators about what they have to do there.

And then in more kind of procedural tasks, you've all received the paper by Alan Buchanan. I think it would be helpful to get some feedback on that; what you find in that to be useful, and where you think that what he has written supports some of the recommendations and conclusions that you're making, and how we can integrate that into the paper.

Then the last thing is that Chapter 2, which doesn't appear in this briefing book because it's relatively unchanged since the last time, we are going to change that to also include a section on use of human biological materials to represent some of the examples that David Korn provided in his paper to give a sense of the historical perspective on use of samples, and include some more information on what we see as the future in terms of use of tissues.

There is also a memo in front of you today which is really based on information that was forwarded to us by Steve Holtzman when he talked to some scientists at his company about what they see as the future of the kind of research they're doing and what their data needs are going to be.

So that's my list. I'm sure that everyone else has their own list of what they think we need to get done. But I would find it useful if we can agree on terminology and definitions so that for the rest of the discussion we all know what we're talking about.

DR. SHAPIRO: Kathi, I think that's very helpful. Obviously, there are a number of different agendas we could order, but that sounds like a very systematic and useful one. Let me just play it back and make sure that I've understood it so I have some sense in my head of how we will structure this discussion.

You want to begin with some agreement on definitions. You've provided some start to that in the last page of the document that we all received. You then want to proceed to the boxes and its various dimensions, which I won't try to describe right now, dealing, first of all, with prospective collection and then dealing with the historical collections that are available, historical in the sense of already collected. And then you would like to proceed to understand a little better about what we may all mean by risks and harms, both the individual, to groups, and so on, and what guidance therefore that we might give IRBs and so on, that set of issues. Then to the community collectivity issue, which we all talk about and the more we talk the more complicated, vaguer, and wispier that idea gets. But we need to at least pin that down and decide what it is we want to do with that. And then deal with the material that Alan has sent, and what we think about that. And then Chapter 2, which you may want to talk about if we get that far down the agenda.

That seems very appropriate to me. I'm sure there's more than one systematic way to go at this, but that seems like one.

Tom, does that seem sensible to you?

DR. MURRAY: Yes. I think that covers my list very well. I have some questions and I know Carol wants to make some comments.

DR. GREIDER: Only if we're going to be going into some of the substance.

DR. SHAPIRO: Yes. Well, I hope we're going to get started right now. I just want to go down and see if that's okay as an agenda to proceed.

DR. MURRAY: That's fine.

DR. SHAPIRO: All right. Let's start then with the definitions. To remind all of you, it's on page 5-15.

DR. HANNA: Would it help, I have an overhead.

DR. MURRAY: Yes. It certainly would be helpful for the people in the audience to know what we're talking about—if that's something we want to happen.

PROFESSOR CAPRON: May I ask a question precisely on this. As we work on documents now which are marked as working documents and so forth, are we making these available—I didn't check the table outside—for people in the public as we go along who are sitting here trying to understand what we're talking about?

DR. SHAPIRO: Let me turn to staff to find out. I just don't know.

MS. HYATT-KNORR: So far, we have not made the drafts available.

PROFESSOR CAPRON: At some point we need to have a discussion of this. We got ourselves in terrible trouble on the cloning report, as it turned out, that we were having discussions and I was not aware until our last meeting that the people who were coming to hear the discussions, including the press, were trying to figure out what we were talking about from the oral comments on something they hadn't read. We're a public body. When we have staff drafts that are going through the process before meetings, of course those have to be worked out by the staff. But once we have a public meeting and are meeting in public session to discuss a document, it has to be understood by everyone that they shouldn't take this to be our final document or say it's our conclusions, as the top line on every one of these says. But I don't understand why they aren't available to the people who come to this meeting or anyone else who wants to see them while we're working on them. We're supposed to be a public Commission. We can only benefit by having people understand what we're doing and not trying to parse it together like something from a Delphic Oracle.

DR. SHAPIRO: Thank you.

PROFESSOR CAPRON: That is not intended as rabble-rousing.

DR. GREIDER: Can I respond quickly to this comment?

DR. SHAPIRO: Yes.

DR. GREIDER: Although I agree in principle with everything that you just said, Alex, there are a number of things that I feel as a Commissioner which I have gotten as a draft document that I've never seen before in my life. I would feel very uncomfortable if these were handed out as a draft document to the public as something that NBAC is working on when I've never seen them before.

PROFESSOR CAPRON: Well, we aren't working on them. It says right at the top this is a draft document developed for, not by, for the National Bioethics Advisory Commission. It does not represent conclusions and should not be cited or referenced, I guess cited or referenced as conclusions. I mean, obviously, anybody can quote from it. Right now we're going to have this up on the board, and someone who is really good at shorthand can take that down and write about it or go to a class and talk about it.

DR. SHAPIRO: All right. Your point is well-taken. Let's just get on with the work here.

PROFESSOR CAPRON: Well, are we resolved that we're going to do something in the future?

DR. SHAPIRO: We'll try to do something. I'm not resolving anything right now until we get a chance to talk to staff about it.

Let's go to the definitions.

DR. GREIDER: First, I'd like to apologize to my fellow Commissioners because I wasn't aware that we were going to be dealing with this today and I haven't thought about it as carefully as I would like to before discussing it. But I would like to turn to some of the definitions, and I absolutely applaud the idea of trying to put some information into these boxes since we've been trying to do that for a number of meetings. But what I'm going to give you is some quick impressions that I have having looked at these definitions. I would like to be able to give more definitive suggestions and hopefully I can do that tomorrow.

And so let me give you just a couple of quick impressions that get to the issue of these definitions, and that is these definitions Kathi took from the reorganized table where she renamed a number of the categories that we had in the past. And one of the distinctions that I felt that we had made in our other meetings that I thought was a big step forward was to refer to the way in which tissues were used rather than the tissues as entities sitting somewhere. Zeke had

suggested to us that we use the language of tissues that are used in an identifiable manner, or used in a coded manner, or that sort of issue. And we've now changed back to the sort of historical definitions that many of the previous people had before us, which is referring specifically to the tissues themselves.

And since this comes out in the definitions, I would like to see some rewording of the actual terminology. For instance, the first one, unidentifiable sample. That I think should be something along the lines of a sample that is used in an unidentifiable manner. And coded but untrackable samples, I think a sample which coded so that it is untrackable. Something along those lines. I'm sorry I don't have exact language, and I'm happy to help work with it. But I feel the direction that we had moved in, and I don't see that reflected in the language as has been rewritten.

DR. SHAPIRO: David?

DR. COX: This is a very contentious point, what you're bringing up now, Carol. The genetics working group I think very rightly realized that how things are going to be used is a very useful way of looking at things. But at our last meeting, we had a discussion that I'd call the "red face test," and that is, if you have things that you can identify and you say that they can't be identified, people are going to look at us and wonder what the hell we're talking about because it does not pass the "red face test."

If you have something that you can identify and you say you can't identify it, that's garbage. So that we can incorporate, in my view, the concept of something in terms of how it's being used, but I can't describe how strongly I feel that if a tissue can be identified, that we cannot define it as being not able to be identified. That's a very strong position, I realize. But I put it up just that strongly so we can have a really clear discussion about it.

DR. SHAPIRO: Tom, then, Alta then Alex.

DR. MURRAY: We made progress last time and I'd rather not have to go over everything from last time. I think actually Kathi's definitions capture key distinctions. Now, I may want to label differently and others may want to provide a different label to them. I want to just make two points I guess here.

One is, in response to David's point, no one is failing the "red face test" in anything that we're proposing to do here. An advance I think we made at the last meeting was to distinguish between those situations in which—I think we had four categories. One category was in their current state of storage there is no identifying information. There's insufficient information with these tissues to know from whom they came. That's category one that Kathi calls it "unidentifiable" here. We can decide what labels to use.

The second category is, in their state of storage, the tissues have identifying information with them. The tissues go forward with perhaps some concurrent information but insufficient to identify the person and there is no backwards link, there's no code or any other thing that would permit you to go back and tell who it came from. So that's her second category. She calls it "coded but untraceable." I used to phrase it something like "identities unrecoverable."

Number three is, again, the information has gone to the researcher without specifically identifying information but with something. There may be some kind of—Kathi calls this one "coded but traceable"—there may be a way to get back. Perhaps there might even be a code held in the Grand Cayman Islands or something, but somebody could potentially make the link. We want to be clear about that.

And the fourth one is where we know. The information that actually goes to the researcher includes sufficient information to identify it.

Furthermore, in samples that are not identifiable; we mean at least two things: One is there isn't specifically identifying information going with them or available; and we also mean, number two, that the context in which you get this information wouldn't permit you to identify, and we used examples about that. Sometimes you can identify because you know the nature of the repository, there are only three cases, and you can figure out who it is. That would not count as a "not identifiable" tissue.

I hope we can still work with those four basic categories. I think Kathi has captured them here. Kathi wants to say something.

DR. HANNA: Yes, I just want to add that I can't take credit for the terms "coded but untraceable" and "coded but traceable." Those actually came from Zeke.

DR. MURRAY: Okay. So we'll either praise or blame Zeke today for the particular terms.

[Laughter.]

DR. MURRAY: The second point I want to make is a very quick conceptual point. Philosophers of language worried about this decades ago, and that is, do we want to make use of commonly available terms but then make them fit around the concepts that we have which do not necessarily coincide with the current use of these terms? In that way, do we want to reform the language, and then hope that people will understand what we're saying? Or, alternatively, do we want to introduce new terms into the discourse that we think have two advantages: (1) they better capture precisely what we mean, and (2) they're unlikely to be confused by being assimilated into the old uses of the term? We need to make a call on that. I don't have any particular view standing here today as to which way to go on that. But we just need to be conscious that we need to make that decision.

PROFESSOR CHARO: First, I feel like the discussions around our characterization of the situations have been particularly heated, in part because many of us are guessing what the substantive rules are going to be for each category. And so by manipulating the nature of the categories, we feel like we might be manipulating the outcome of the rules. If we imagined that a sample that's understood to be used in an "unidentifiable" fashion will be free of most of the kinds of regulatory constraints that flow from an IRB, then we have a big investment in what goes into the category of "unidentifiable."

I would like to urge that we keep these things very separate because with this set of definitions, which I find very useable, we can fiddle on the exact descriptions within them, but I find very useable, we don't have anything in there yet about the manner of the use by the various kinds of investigators in terms of both identifiability and the actual risk that it poses to the individuals from whom the samples were taken, since identifiability is not going to be synonymous with risk in all case. And so I would like to urge that we not go back to the effort to define based on use, stick with these, but to be very attentive to the fact that the tentative contents of these boxes is still entirely up for grabs.

We've yet to actually even fill in for the clarification of all the way the current regulations operate in each of these boxes. And, in fact there was something that was distributed today that will make that easier to do, to give people a starting point for what exists and what would have to be changed, added to, deleted, etc. But that there's plenty of room for blood to flow over the actual rules that will apply without having it to flow over these definitions.

DR. SHAPIRO: Alex, then Bernie.

PROFESSOR CAPRON: I agree with Alta. I was going to suggest that we consider recognizing that we are most concerned about—I do think there is something to Zeke's point that Carol is pressing, is samples as they are used in research and the samples can be unidentifiable either because they were collected without personal identifiers, or because they have been provided to the researcher without any coding that links them to the identifiers in the storage base. But it may be advantageous to say that there are those two differences.

I want to urge that we drop the second sentences from the first four definitions. These I do not believe they are being used in definitive fashion. It would be possible to say that's an implication and that belongs in commentary on the text as a reason for distinguishing or as a consequence of having this category. But if people are agreeable, I would like to urge that we do that.

I would also suggest an alternative wording, as I am concerned about the kinds of things that David has raised, for the "unidentifiable sample." If I can read this and if it makes sense, then I'll get it typed out and provide it to Kathi or whatever. "'Unidentifiable sample' means that no personal information is attached to the sample through which it can be linked to the person from whom it was obtained." And I say that because the ultimate point that was made to us is if you do a genetic test on the person, and on the sample, after the fact, you could, in fact, say, oh, this turns out to have been his sample, but you didn't know it at the time. But no personal information as opposed to the biological information is attached to the sample. If that's agreeable, I'll provide it.

DR. SHAPIRO: My understanding of what you said, Alex, it is perfectly consistent with what's here and is a little clearer. I agree with you.

PROFESSOR CAPRON: It was just meant as a clarification, not a substantive change.

DR. SHAPIRO: I agree with you.

We have a lot of people who want to say something and I'm having a hard time restraining myself. But David, you were the next, then Bernie.

DR. COX: I just wanted to address a point that Tom made with respect to language. I really applaud that statement. I think that we can use language in a very powerful way to help clarify the situation but that we have to be really careful that it clarifies and doesn't leave opportunity for people to use it in an ambiguous fashion. That's what I'm most concerned about. And so I'm not wedded at all to the terms that people have used in the past. But my point is, and I actually completely concur with the direction that Alex just went, if we can make these definitions sort of bulletproof, then it is very difficult to have those definitions be misinterpreted, and then follow with what Alta said in terms of how we use those definitions in a creative way.

DR. SHAPIRO: Thank you.

Bernie?

DR. LO: I agree that it's really important we get definitions that are clear and make sense. I have a couple of suggestions with the first four. One, it seems to me the issues that are pertinent to whether a given sample falls into one of these four categories are, first, how is it stored, with or without identifiers; how is it passed on to the researcher, with or without identifiers and what kind of identifiers; and third, if it's in some sort of code, what kind of code, who holds the key to it, and how easy is it for the researcher to crack.

I think the third and fourth, we're trying to draw a bright line and it's really a matter of probability. That if you really work hard enough and ask enough people, you probably can crack something in three, but it's going to be a lot more trouble in four. So I think that it's almost I see sort of a grid with several, that these are the rows and columns of yes, noes.

And, finally, I'm concerned about—I'm not sure why we're saying "traceable" and "identifiable". Are we meaning them to be different, or do we really mean coded but identifiable with a lot of effort but not easily on the part of the researcher? So if we're going to use two different terms, I'd like to see some clarification of why we say identifiable in some and traceable in others.

DR. SHAPIRO: Okay. I've got a number of people here.

Carol, first.

DR. MURRAY: Could I just say I don't think we should be wedded to the terms "coded" and "traceable" here. They're Zeke's candidates to express what we want to express but we should use the term that strikes us as most effective.

DR. LO: Right. I was just saying that to use both traceable and identifiable without explaining creates confusion for me.

DR. SHAPIRO: Carol?

DR. GREIDER: I just want to respond to the idea, getting back to this sort of meat issue about whether we talk about the sample or whether we talk about how the sample is used. I want to assure my colleagues that I don't have any particular agenda here that I'm pushing, and I haven't decided that there's a particular box things should go in, or that sort of issue. It really is just an issue about trying to be as honest as I possibly can about what we're really talking about.

When I look at this table I ask the question, is this really a sample we're talking about or is it how we use the sample? And it's really that simple a question that is my concern. I'm generally happy with the four areas and I think we made a lot of progress at the last meeting, and I agree that we had muddled some issues that we unmuddled at the last meeting by making these four categories. But I still come down to it and I look at this number three, "coded but untraceable sample," that doesn't really refer to a sample, it refers to how you're using the sample. And so I just have a very hard time thinking about something that exists physically versus how you're using it, and that's my only agenda that I have.

DR. SHAPIRO: We do need to talk this out. I do think there is a distinction and I do think, my own sense of this, Carol, is that the distinction Alta made is actually very helpful. It may require that we change this table in some way so the table wouldn't look the same any longer, that's a discussion you have to have, but I think it really is useful. I think

we have to get the definitions right. A number of suggestions were made. Bernie's suggestion that maybe we don't need two words, maybe one will do; that is, we can use "identifiable" and "unidentifiable" rather than "unidentifiable," "untraceable," as if this were a new concept being introduced. I think that maybe helped. We have to work on other things in these definitions. But I do think that distinction is actually a helpful one that moves us forward.

DR. DUMAS: The distinction between how the sample is used and what we mean by certain terms that we use?

DR. SHAPIRO: That's right.

DR. DUMAS: And I think we need to keep those two things separate.

DR. SHAPIRO: That's what I understood to be Alta's point.

DR. DUMAS: Okay.

PROFESSOR CAPRON: Excuse me. Could I add in response. Would it be helpful to say that if we are going to look at this as our major concern as the sample in the hands of the researcher, then a sample can be unidentifiable because there was no personal information attached to it, or because it has been provided in a way which is coded but not linked with or traceable to the original. In other words, to recognize that you come into the point of research from two different ways. Alta still says no.

PROFESSOR CHARO: I'm shaking my head because what happened in—

PROFESSOR CAPRON: I know, this is the—

DR. SHAPIRO: Larry had his hand up first.

PROFESSOR CAPRON: That's absolutely right. I apologize, Larry. You're right. I apologize.

DR. MIIKE: Maybe it's the advantage of me being at the last meeting by phone with a terrible connection—But I agree with Carol. I'll tell you why. Alex says changing of the definition of number one makes all of these compatible with how it's used. And it really is how it's used. Because you may have a repository but you're going to take a little bit of that and you're going to code it or you're going to make it unidentifiable, and that's what we're worried about, that little piece, there is or is not a connection to the original repository.

So it is the way in which it is used. That is, once you change this little front definition that means the samples were collected, we accept Alex's definition, all of these define the use. I think it's more important to do it that way than to talk about how it is originally stored.

DR. SHAPIRO: I'm not sure that I've understood what you've said. I really think that the issue, to the extent that I've understood it, is that we can describe the state of the sample without knowing how someone is going to use it.

DR. MIIKE: No, no, no. If you look at any of these "coded but untraceable" or "coded but traceable," that is after you have applied something to the samples for the researchers to use. It is not sitting there coded but untraceable or coded but traceable; it's the application to the stored sample that makes them then fall into these categories.

DR. SHAPIRO: Alta?

PROFESSOR CHARO: By the way, I want to reserve at least a moment to talk about the other definitions on review and consent. I feel like another source of the debate here may stem from the fact that we're dealing with two possessors of a piece of tissue—the repository and the investigator—in what is now I think the paradigm we're all holding in our heads, which is of a repository that sends samples to investigators. And to complete the paradigm, I think we're imagining a sample of tissue large enough that they can cut off slices and send individual portions. That's one. Let me just hold that one in my head for the moment for the purpose of discussion, okay.

So that when the repository sends something to an investigator, and, for example, may send it to an investigator with no personal information attached to it and with no code attached to the slice being sent to the investigator that lets the investigator individually, with the cooperation of the repository, recreate the links from that slice, to the larger sample, to the original donor, we're trying to capture in the definitions the state of identifiability here from both the perspective of the repository and the perspective of the investigator. And I think it's the effort to capture both

simultaneously that is leading to such debate.

It's possible that where Carol and maybe Larry, because I also wasn't quite sure, but where Carol is coming from is that the sample can be identified at the moment at which it is in the investigator's hands as identified or unidentified. It's got a name, it's got a code, it's got nothing. And the status of the slice that the investigator has might be different than the status of the larger block of tissue back in the repository, right?

Dr. MURRAY: That's the key definition.

PROFESSOR CHARO: That's key. And maybe this is where you're calling it the use of the investigator. But, in fact, it's actually the status of the slice. It's also the status of the sample. It is not a use. It's the sample itself. You've now made two samples out of one and they've got different identifiability status.

DR. MURRAY: We're all there. All right.

PROFESSOR CHARO: I also feel like I was the last one to figure it out. But what I'd like to end with though is that I don't believe that we can fully appreciate the parameters of risk that are created and the parameters of benefit that are created by virtue of degrees of identifiability and degrees of traceability unless we constantly see these things in the context of the repository and the investigator simultaneously. I don't think that talking about the sample at the moment that it's in the investigator's hands without reference to the larger block of tissue back in the repository can let us fully understand the significance of that sample in the investigator's hands, because of the example that was raised last time of the investigator has 100 samples that are totally unidentified to him or her but if all 100 universally show the BRCA1 gene, the investigator could, in fact, let the repository know you gave me 100 BRCA1 gene samples, and the repository, by virtue of the fact that there really is still information left, could, in fact, identify— I defined the paradigm. I'm only working on one hypothetical at a time. Could we go back to those original 100 people. And that's why I think that it is still worth the effort to try to capture in our definitions the collective effect of these differing identifiability statuses, of not uses but of configurations of tissue and bits and pieces of the tissue which collectively represent what you're calling a use.

DR. SHAPIRO: Okay. Tom, Carol, then Bernie.

DR. MURRAY: Alta, I want to affirm what you just said and say that that is why when I talk about tissue for which identity might be recoverable, there are two ways. One is that there exists some kind of intermediary code, and the second is context. And your example of all the 100 samples out of a bank of whatever, that's a case in which the context might make some sort of identifiable.

PROFESSOR CHARO: Right. But here would come under what's category two, because it came to the investigator without a code and, under the current regulations, would be considered exempt from IRB review.

DR. MURRAY: That may be true.

PROFESSOR CHARO: Right? And that's exactly why it's worth keeping the category separate, because we may want to revisit is the current regulatory status of this particular phenomenon adequate. And it may be that it is because these situations will be rare enough that it's not worth worrying about.

DR. MURRAY: But in a sample where there were a 200 tissue sample repository and 100 went forward and they all had the mutations in BRCA1, then the context would say I suppose you have a sufficient—well, I don't know, actually. I want to think about that a little bit more.

DR. SHAPIRO: Carol?

DR. GREIDER: So I agree with everything that you just said, Alta. The reason that I was focusing on the second half, if you have how they are in the repository and how they are in the investigator's hands, was because that's going all the cases that you're going to look at where you're going to try and be protecting people, what the IRB is going to be looking at is going to be that group. But I don't have anything against trying to broaden our definitions and include some kind of a definition that would take both of those into account. But I don't think that just dividing these into the four definitions that we have does that. I think that we get back into a muddled situation in this using these definitions here.

So if we can come up with additional definitions or additional language that does incorporate both of those

things, that's fine. I'm not particularly wedded to the use of terminology. But I just have a very hard time sitting here imagining a particular sample in somebody's hands being considered identified or nonidentified when, in fact, it is identified back somewhere else. All I am saying is that I don't think that all of our definitions take both things into account simultaneously.

DR. SHAPIRO: Let me ask a question here, and I do have others, Bernie, then Eric. If you look back, Alta, you're using your structure, the initial primordial description of the sample that exists in some bank somewhere or will exist in some bank, they're either identified or they're not identified, right. They either have identifying information or they don't. There are no other possibilities here the way that's defined.

PROFESSOR CHARO: Right.

DR. SHAPIRO: If they are unidentified, then they have no possibilities but to remain unidentified. And no matter how you use it, when you use it, what it's for, you just have unidentified samples passed from repository to investigators and you have a series of decisions to make of what the appropriate use of that is.

If it's identified, falling in the second category, then there are some alternatives regarding what Bernie would call probabilities, that get set up here, how hard it is. They get passed on to researchers and then the question is, what kind of wall do you build between the researchers in the first stage and second stage of this? Does that capture what you said?

PROFESSOR CHARO: Yes. That absolutely could be done and one could describe the various ways in which tissue becomes identifiable through demographic information, through name and address, etc.

DR. SHAPIRO: Right. It's not only name and address, there's other kinds of things.

PROFESSOR CHARO: And all of these things would then be associated with probabilities that one could actually get back to an individual.

DR. GREIDER: So there are two kinds of tissue—identified and not identified.

PROFESSOR CAPRON: At the first stage.

DR. SHAPIRO: Repository tissues are of two types. The research tissues are of four types.

PROFESSOR CAPRON: Correct.

DR. CASSELL: Make the distinction.

PROFESSOR CAPRON: That's right.

DR. SHAPIRO: What I was going to suggest is that if you sort of look at this table, we're not at the table yet, I apologize, Kathi, for skipping off the definitions for a second, the first one is "identifiable." You've thought of another column in here, right, which is sort of the repository stage or something.

DR. SHAPIRO: You would have "identified," "unidentified," only two. Then the "unidentified" one would break into a series of things.

DR. GREIDER: No, the "identified" one.

DR. SHAPIRO: Bernie?

DR. LO: We're reinventing history here, because the old, old terminology was "anonymous samples" which in the repository were not identified and, therefore, never could be identified except for going back to the DNA. Then to follow Harold's model, if it's identifiable in the repository, you still have a bunch of options. You could totally strip it, anonymize it so that the researcher could never go backwards. You could code it, and you could code it in two ways, either a way that makes it very, very difficult for the researcher to trace it backward, although the keeper in the repository might be able to go forward, or you could code it in a way where the researcher in a sense makes up the code. Or you can keep it completely identifiable all the way through.

DR. LO: But the old-fashioned language of anonymous versus anonymized really tried to capture the duality of what we now have in our unidentified samples, which speaks to what Alta and Harold picked up on. So I don't know if

we're going back. I think we all want to do something new and throw out what everyone else has said before, but why?

DR. LO: The older language may actually be better.

DR. SHAPIRO: I want a rescue, if possible. Eric?

DR. CASSELL: Just picking up on what you said and what I was thinking as Alta was talking is in the report you make it clear that the repository has responsibilities, that they have ethical responsibilities in regard to the tissues in their keeping. I just got an e-mail about Cornell's repository in which they say, "Provide researchers with a reliable, ample supply of procured human tissue and all the data for interpretation and experimental--blah--but protecting the patient's right to privacy and confidentiality." And if we just classify that's their responsibility, then after that you've divided it up and then you're off and running with the other stuff. But let's make it clear there are two different things.

DR. SHAPIRO: Kathi?

DR. HANNA: I just want to draw everybody's attention to the two paragraphs on page 5-4, lines 11 through 25. If you would take a look at that tonight and let me know specifically—

DR. HANNA: This is on page 5-4, lines 11 through 25. This is where I had written it, in a simple way, samples fall into two categories, identifiable and unidentifiable, and then I talk about how within the identifiable category—I'm sorry, you have to continue on to the next page—there are three subcategories. So if you would take a look at that and see if that makes sense. We can always change the words but I think what we've just talked about is there.

And I want to just make the point that for the person who donated the tissue, whether it is in category two, three, or four might not make any difference to them. So I just think we keep talking about the pathologist or the investigator, there is a third party. In the first category, obviously they can't be identified; so we don't know who they are, they don't know that research is being done. In categories two, three, and four, when you get to discussions about protections, the third party who is the patient or the research participant is a third party. And so I'm just reminding you.

DR. MURRAY: Do you think two is equivalent to four from the patient's point of view?

DR. HANNA: No, no. I'm just saying that if it's identifiable at first, the sample can become two, three, or four depending on how it's used in research. So when you talk about protections, you're trying to protect, I'm assuming, the donor of the sample, correct? So, I'm just reminding you.

DR. MURRAY: Right. And virtually all the samples we've identified are in their original state they are identifiable. Category one, tissues in their original state which are unidentifiable, apparently are rather rare.

DR. HANNA: Right. I'm just saying that for two, three, or four, you can have one sample that can fall into any of those categories depending on how you use it in the research.

DR. SHAPIRO: Excuse me. Bette, I'm sorry.

MS. KRAMER: Mine is a point of information more than a comment. Going back over the months of discussing these definitions, I think we were at this point several meetings ago when David, and correct me if I'm wrong, you made a fairly strong statement that in your opinion any sample that was coded in such a way that it was untraceable, that's what we were then calling it, could, in fact, be traced, that a researcher hot on the trail of something would trace it. And you raised that caveat for us and I think that's when we began to reexamine some of these definitions.

Do you find these definitions acceptable, or do you have that same concern?

DR. COX: Absolutely. In fact, starting off by talking about these as being—the way Harold and the way basically everyone has been saying it, it's not just one person, is that you have samples that are either unidentifiable or they are identifiable from the point of view of the repository, from the big slab of tissue, right? I mean, that's the viewpoint that I'm looking at this from, not from the slice, but from where the slice comes. Then, if it's not identifiable, just the way Harold said it, you can't identify it. The person doesn't know it's theirs, you don't, nobody knows it's theirs. And as Tom correctly states, that's a small subset of all the things we're talking about.

Then we have this other stuff that is identifiable and then you can do different stuff with that. I think that's where we can be creative and that's where all the discussion is. But I'm looking at it from that perspective. And if we

go from those definitions, then I'm a really happy camper. But what we do with that, that's now what we....So I think it's a three-way street here.

DR. MIIKE: Harold, can I ask David a follow up question. Given that you have unidentifiable/identifiable to begin with, and then we have these three ways of generally distinguishing the identifiable, following up Betty's question, do you feel comfortable treating those differently, or do you think they are all going to be identifiable in one way or another?

DR. COX: That's what I'd like to have most of our discussion about. I don't have a firm position about that, but I think that's where the meat of the discussion is and that what we can't do is not have that discussion by already putting things in one category or another. That's what I'm so heated about because I want to make sure that we have that discussion. And if we already preclude the discussion by how we define things, then I'm very concerned about that.

DR. SHAPIRO: Carol, then I can't restrain myself from making another comment. But, anyhow, Carol?

DR. GREIDER: I really like the way that Harold phrased this in terms of there being two categories, "identifiable" and "nonidentifiable," and then subcategories off of the identifiable. I think that will get us all in the same camp. And if we're all in agreement, I mean if David and I are in agreement here, then we've made huge progress.

Given that then, getting back to the definitions, I would suggest that the first definition could be "unidentifiable sample" and then all three of the following ones should start with the term "identifiable." Perhaps my suggestion for number two would be "identifiable, but used in"—blah, I'm not sure of the terminology here. And the third one would be "identifiable, but used"—this way. And the fourth one would be "identifiable, but used"—this way. That's a suggestion. But that all three of those other ones should start with the term "identifiable" if that's what they actually are.

DR. SHAPIRO: I'm not sure what I would say either takes us backwards or forwards, but I'll give it a shot anyway.

DR. SHAPIRO: It probably doesn't move us one bit. I agree, we've got these two categories initially, they're broken down. I think the identified sample really, as it exists in the repository—that it's identifiable, it can then be passed forward in actually four different categories, not three. Because it could be passed forward anonymously; it could be anonymized. Passed forward with no information.

DR. SHAPIRO: Okay. It can be passed forward, all of these are passed forward with various levels of information.

DR. GREIDER: But there's disagreement about that.

DR. SHAPIRO: Okay. Just a minute. The issue is the information content with what you pass forward.

DR. SHAPIRO: And they differ by the level of information content. And that makes it either harder or less hard, as Bernie said, to get your way back. It all depends on the amount of content. Now some can be passed forward from its identified sample with no information content; that is, no information that enables any further identification. And then it is a question of how many different categories of information you want to identify here for purposes of operationalizing a set of rules. You've got at least two; that is, you could pass them forward completely identified, you can pass them forward completely unidentified. And then the question is do you want any further distinctions regarding the level of information and what that means.

PROFESSOR CAPRON: I lost how that's four rather than three.

DR. SHAPIRO: It's just a question of the amount of information. It may be some are passed without information, some with full information, that's two.

DR. DUMAS: Some without information but the information can be obtained.

DR. SHAPIRO: That's right, that's the third.

PROFESSOR CAPRON Let me understand then. If the request is for samples from people who have had breast cancer, biopsies from people who have had mastectomies for breast cancer, that's with information automatically, as opposed to just send me any ten tissue samples you have.

DR. SHAPIRO: And I think for me the hard question I can't quite get my head around yet is how many distinctions in there are worth making for generating guidelines regarding use. I don't have an answer to that. I just have a question in my head but I don't have a way of dealing with it yet.

Tom, then Bernie.

DR. MURRAY: I may do this more than once in our conversation about tissue samples, which is to just try to state as concretely and succinctly as I can advances that I think we've made in our understanding. Alex I thought offered something very helpful when he said, look, when it comes to thinking about "identifiable," we're talking about personal information that may accompany the sample. I think that's an advance. It gets rid of the confusion with genetic fingerprinting and such. That's good. Everybody I hope agrees with that, that we should use that as a sort of key phrase in our various definitions.

Alta I thought had two very important points that I want to stay with and try to articulate, if I can read my handwriting. Number one, that I think she has shown us that even if one guarantees that no individually identifiable information goes forward and there's not even a code a links back the samples, that there are at least some circumstances imaginable, whether or not they'd actually ever happen, under which one can imagine an individual actually having some risk of harm from having their samples forwarded; her example of 100 samples going forward, all of them having the BRCA1 mutation, and we know the 200 people who were in that bank, that means there's a 0.5 probability of any individual who contributed tissue to that bank has the BRCA1 mutation. But I just want to make the point that there's a distinction to be made here. The distinction is between figuring out what category to put it in and just descriptively in terms of is it identifiable or not. That does not exhaust the possibilities for being at risk. That's the distinction in there. Okay?

DR. MURRAY: So I would say that in the case that Alta described, that person is not identifiable and their tissues are not individually identifiable. That does not mean that they are therefore protected from all possible or imaginable forms of risk. In practice, they might be, but that's a sort of question one might pose to an IRB, to say, look, does this kind of guarantee of lack of identification actually provide a guarantee, provide protection against imaginable risk.

The other point that Alta made that I thought was very important, one that I'm going to try to remember, and that is as we just discuss the categories that are meaningful, let's try to avoid immediately reading into them our policy recommendations, because then we're going to want to jiggle with the categories to make them follow. Let's get the categories straight. I think these are good categories. I like the categories. I'd like us to work with them, realizing that within them we may make some varying recommendations, including there might be two different sets of samples belonging in the same category, we might have somewhat different advice.

The last point I think was progress was Harold's point, who phrased succinctly what many of us have been sort of trying to say, and that is you've got to think the samples as they exist in the repository--and I think, Kathi, for all of us, we're going to need a definition of a human biological material. And I'm going to suggest, at least tentatively, that we sort of use that and define that, sort of make that our keystone for what is held in the repository, that's the human biological material, and that we try to reserve the word "sample" for its use by researchers. At least maybe we need the phrase "sample as used by a researcher," or "sample as forwarded to a researcher."

So there's two of the former, right, to either have that personal information or they don't, and then there are four of the latter. I hope we can all agree on those. I think those conceptual tools actually take us quite a bit forward.

Tom, it seemed to me that Harold had introduced a complication, however. I'm just not sure what we do with the four. I think our definitions have to do exactly what you say, we have to have the human biological material referring to repositories, and we have our two definitions of identifiable and unidentifiable, and then we say as used in research, material passed on as a sample can be of several different types.

The complication that he introduced was, we can talk about linked codes, unlinked codes, and identifiable or unidentifiable, but his suggestion is that sometimes it's not the coding information that's important, it's the biological information that's provided along which is a form of identification because it narrows down the group from whom the tissue could have come.

My concern is not with Machiavellian people trying like investigative reporters or something trying to ferret out

where did this semen come from. The question in all of these cases is for what may in a research context seem like good and sufficient reasons, are people in a position to link research findings with an individual or a small group of individuals who have a high probability of being the person identified where that information may be unwanted or harmful in some way and at least wasn't something that the individual may know has been found out about them. Those are the kinds of concerns that arise.

And so, if it is information, not just the code—in other words, you've said I want these people like this, and they provide it with codes which are not linked to their samples, they couldn't tell you, number one, that I gave you is Mr. Jones, number 475 in my repository, but the ten samples, once you find out about them, if you came back and said we've just got to find these people because they've got something that's so urgent, they could say, well, at least I can narrow it down because I do know from the information that you asked me, the characteristics, that it must have been these ten people. That's an example of something that is unlinked, an unlinked code but it's still traceable.

DR. MURRAY: Well, that would be then number three. That would be identity recoverable.

DR. CASSELL: Potentially recoverable.

DR. MURRAY: Potentially recoverable.

PROFESSOR CAPRON: I just hope we can capture what Harold has brought out because—

DR. SHAPIRO: Exactly that. I was worried about biological information as opposed to the name, address, or that kind of personal information. And it may be an unnecessary complication.

PROFESSOR CAPRON: No, I have a sense that it's probably the very complication that is most likely if the researcher has narrowed down her research to certain characteristics.

DR. SHAPIRO: Okay. Bernie, then David.

DR. LO: Let me try and follow up, Harold, on your suggestion that if we look at tissues that are identifiable in the repository, there are several different ways they can be passed on to a researcher as samples. I'm just pointing out we have two extremes. One is where all the information is passed on, and one where none of the information is passed on. Now Hertz has a very good ad that says there's Hertz and there's not exactly. So passing on all the information and not exactly passing on all the information but coming pretty close.

And that's what typically is done in research is you never use, the IRBs don't let you use the patient's name on all the documents. You've got to give them a code. But I may have a code that 001 is me, 002 is Lori, 003 is Eric, and it's transparent, it's easy to crack. But it protects against just having papers lying on your desk and people peeking. But for all intents and purposes, it is very transparent, the code. It seems to me those two we should put at one extreme saying it's really going to be awfully easy for anybody in an investigator shop to crack the code.

Then you have the other extreme, samples where, short of doing investigative reporting or a full day in a file, you're not going to be able to trace back.

Then in the middle are samples that are coded in ways that don't make it impossible to ever trace that but make it a lot tougher than is the case with ordinary coding as it's understood in the research enterprise. And sometimes you can crack the code because this elaborate encryption scheme with the matching pass words to someone in Antarctica or something, you can go to Antarctica and bribe the guy and get the code. Or, you may be able to deduce it through this kind of elaborate piecing of information the way Alex characterizes investigative reporters.

The point for our purposes is it takes a lot of effort, it's not something I'd just pick up the phone and call someone and say "Hey, tell me who 003 is because I need to get more information." There's an inherent check in the process of getting more information because it's just much more complicated and more difficult, but I still can do it.

Maybe those are sort of the gross distinctions we can make and just realize there are lots of different kinds of encryption that fit in that intermediate category. And we actually, frankly, haven't really thought through how you might construct the system that has those characteristics. But we would should be able to deduce, given that you have such a sample and coded, what the ethical implications are for the type of research.

DR. SHAPIRO: David, then Alta.

DR. COX: So it's really following up on what Bernie said. I'm putting myself in the perspective of the repository now with a sample that's identifiable and thinking about different things I can do with that sample. So one of the things is that I can give it to people so that they will have it be coded but be coded in one of these extreme ways because they never want to have any identifiers, they aren't interested in it, and that they would just like the sample with information that will not make it identifiable.

I, as the repository, can do that in one of two ways. I can give it in a coded way that there was no possible way that I can even figure out what it was. Now there may be some way that somebody could do it, but my intention is to do it in such way that I don't know what's going on. Not only does the people I give it to not know what's going on, but I don't know what's going on. That doesn't mean that somebody at some time couldn't go and figure out what's going on, but it's going to be really hard.

Let me just say, I used to think that this was a pretty straightforward issue, but what I've been convinced is that just the pieces of information that are given out are sometimes more traceable than one might think. So I'd just like to make that caveat. As an example, a piece of information in terms of family structure, if you know it came from a certain city and you can get from that city the names and addresses of all the people and whose related to who, it's very easy to identify that even though I may have made it so that I thought it was very non-coded. But my intention was to scramble it so I didn't know it and the other person didn't know it.

But then there can be another way you can do it. I can scramble it in a way that the person I'm giving it to doesn't know it, but I can easily figure it out. And I'd like to make that distinction from the point of view of the repository and that whether I still can figure it out or not, because I think that's really important from the point of view of everybody—from the point of view of the repository, from the point of view of the researcher, and from the point of view of the patient. So why is it important if I can still figure it out?

Well, from the point of view of the researcher, it's very important because as a researcher, if I found something really interesting, I know that person in the repository can go back and get it. From the point of view of the patient it's important because whatever is done on that sample, the repository still knows it's mine, can figure that out. And from the point of view of the repository it's in the context of both of those people that I still can figure it out.

So it's not saying what the risks are, what the harms are, but me, as a person in the repository, that's a very different scenario for me. And I'd like to make that distinction in terms of how hard it is to do it. Sort of what the intention is. Because I think even if my intention is to make it so that I don't know and the other person doesn't know, now we're talking about situations of, well, how good a job have I done. But it's what that intention is.

DR. SHAPIRO: Alta?

PROFESSOR CHARO: You know, David, I never like to disagree with you because you're so much smarter about this stuff, actually. But I fear that in some ways we're making this too hard because even under current regs in ordinary experiments that don't involve tissue samples where you're doing research that involves having peoples' identities obscured with codes that provide links, a problem emerges about whether or not those codes could be broken, a problem emerges about whether the cell size is small enough that based on demographic information that you are planning to use publicly the identities could be reconstructed. And with regard to biological information, which Harold was mentioning, I remember hearing my colleague, Norm Foss, when we struggled with this at UW say that this is all very temporary because in the future with forensic DNA analysis every sample will be identifiable through direct testing against a national database in which every person's forensic DNA signature has been entered.

And so I wonder if we are failing to remember that there's going to be room for an IRB at various stages to accommodate these issues. One could maintain the kind of traditional distinctions among things that have the name and address versus things that have some kind of coded link versus things that have no codes and remember that in the substantive content that we give to the rules that will follow all the various categories there will be a role for the IRB particularly at the repository to make a judgment about whether or not the request for X number of samples meeting certain demographic characteristics poses a threat of a breech of personal identity by virtue of the cell size or the nature of the demographic information.

But we don't need to necessarily handle all these problems at the level of the definitions, but that they can be left at the level of the substantive protections we build in through the IRBs. And that might simplify our definitional

struggles over whether we're going to define based on whether there's a code versus defining based on the kind of degrees of difficulty of obtaining personal identity, which to me seems like it's going to be impossible since it will be a continuous spectrum of ease; it will never have any bright line distinctions.

DR. COX: No, I wasn't suggesting that be in the definition. I'm completely with you.

PROFESSOR CHARO: Oh, good. So I'm not disagreeing with you. I feel safer.

DR. SHAPIRO: Thank you. Tom?

DR. MURRAY: As I sit here today, once again, I am very, very impressed by how smart my fellow Commissioners are—

DR. CASSELL: And stubborn.

DR. MURRAY: No. I wasn't even thinking that, Eric. At how wonderful they are at thinking of distinctions and complexities, of which we need to be mindful. But I had come I guess to a similar conclusion as Alta; namely that we shouldn't try to cram it all into our categories. To my view, the categories are just a kind of tool to let us take the next step, which is to figure out what the recommendations and policies, including IRB things, ought to be. Whatever set of categories we end up with, I think these actually work fine, have to be able to do two things for us. Number one, they have to be sensible in the sense that we sort of know where to put things. Give me an example, can I fit it into one of these four, more or less unambiguously, can I figure out which it goes into? I think these make the test about as well as any set we're going to come up with.

So then you have the second sort of criteria by which to judge the categories, and that is do they provide a useful first step at organizing our intuitions about what policy implications ought to be and implications for IRB. Not do they exhaust it, because they clearly won't, but just do they provide us a useful kind of organizing way of getting to make the next step, which is going to be tougher actually.

Those are the only two criteria I think by which to judge the categories. I happen to think these work well. I'm going to ask you to decide whether you want to do that or not tomorrow morning. We really should make a call because I think we need to.

And I want to actually, Harold gave me a kind of silent consent a minute ago, assign a little homework. Kathi asked us to read just about one page. That won't take long; I hope everybody can do that assignment. Alta had distributed a memo from Gary Ellis which also won't take more than a few minutes I think to review, just to give us a sense of—it is dated 17 April 1996 to OPRR staff from G.B. Ellis. It's a frequently asked questions sheet here with responses. That's going to be quick.

PROFESSOR CHARO: With little pictures.

DR. MURRAY: Yes. And I think we actually need graphics to make some of the points. I'm wanting to think in terms of pictures. I think that will help when we actually do the report. The third homework assignment is a little tougher. I hope you've had a chance to read Alan Buchanan's excellent essay because Alan really cuts through a lot of jargon and gets us to think about what actual interests are implicated on both sides in these various decisions we're going to make. Even if you just skim Alan's paper to get a sense, this will help us tomorrow because I think we are tripping ourselves up on issues which are not irrelevant but may not be at the heart of it. And so we need to focus on what specific interests we think we need to be protecting that are implicated in certain of these situations, what interests in terms of research need to be respected and advanced, and how are we going to weigh them. So, if you'll accept them, those are my suggested homework assignments for tonight.

DR. SHAPIRO: I like them. Larry?

PROFESSOR CAPRON: I understood implicit in Tom's comments just now was that we are not going to spend further time talking now about the first four definitions. I wanted to ask a question of the drafters, however, about the last definition. It says "general consent means consent to future unspecified research use of the sample." Now, "benefits and risks are specified regarding future research use but not regarding any specific protocol." I don't quite get that.

If it means the risk of being in a research use, of having a sample used is specified, that seems to me to be

already stated in the first sentence. If it means something more than that, I thought the whole message we got from researchers was until you knew what the research was you really couldn't say anything about what the benefits and risks would be. Having your tissue used for one test might have no research risk, no personal risk, having it used for something else could be very risky. So I don't know what that sentence means.

DR. SHAPIRO: I have a comment on that, but Kathi?

DR. HANNA: Just my response is the last three definitions are the definitions that have appeared on the boxes since September. So I'm glad we're finally getting around to talking about them. But these are unchanged from what were on Zeke's boxes.

PROFESSOR CAPRON: Right. What I'm asking now is, what do we think we're saying here? This isn't criticism of a drafter. Now that you hold them out here very usefully, we stop and look at them, when I look at this one I don't understand what that second sentence means.

DR. SHAPIRO: My own view of that is, and it was a point I guess made by Alan Buchanan that actually makes that in his paper, the second sentence is not operational in any real sense. So I think it could be dropped, is my own view, as Alan suggests.

DR. MURRAY: What Buchanan writes about—blanket consent—I think is relevant to this.

DR. SHAPIRO: Why don't we spend a few minutes, we were supposed to adjourn five minutes ago, but I just would like to spend a few minutes looking at those bottom four definitions and see if people have some comments, suggestions, etc.

Bernie?

DR. LO: With regard to the administrative review by the IRB, I would suggest an addition—first of all, it may not be the IRB chair, but somebody delegated by the IRB. It is not just the identifiability status, but also the prospect of community harm which comes into the part of the table that was truncated from the previous page.

DR. SHAPIRO: I have no problem with that, except that I do want to get some discussion, now is not the moment, on how we're going to deal with this whole idea of community and so on. But I have no objection right now. I understand the point.

Alta?

PROFESSOR CHARO: I think I've got more trouble with the two phrases that were recurring from the earlier incarnations, "administrative review by the IRB" and "full review by the IRB." They don't match anything that exists in the current regulatory language and, as a result, I find, as somebody who works with the current regulations, as most people who work with the new things we recommend will be, that they are tremendously confusing.

The current system is one in which investigators make the first cut at determining whether or not they need to even go to the IRB. And if we want to change that, we can change that, but I don't think you want to call it "administrative review by an IRB."

The second thing is that when it goes to the IRB a decision is made about whether or not the substance of the research is exempt from IRB review. And that's what I think Zeke meant by "administrative review by the IRB." That's not administrative, that's review by the IRB. And whoever is designated in that institution according to their multiple assurance to make that decision makes that decision. It's often the administrator rather than the chair.

If it's not exempt, it then goes to the IRB for review. And this is where I think Zeke was imagining the phrase "full review by the IRB." But that obscures the fact that there are levels of rigor in IRB review, including eligibility for review by only a portion of the IRB. And I don't think he intended to eliminate all of those various nuances in the concept of IRB review. And by putting in a phrase like "full review," it implies that we're requiring that the entire committee has to be meeting and reading the protocol together and voting on its acceptability, all of which are regulatory rules for certain categories of research.

I would like to suggest we dump this stuff because it's more trouble than it's worth, and focus as we go through tomorrow the actual content of what we want for each of these boxes, on what the current regs say and then identify

specifically where we would like to change those regs, and, at that point, see whether a change in vocabulary is necessary or whether existing vocabulary is sufficient to convey our meaning.

PROFESSOR CAPRON: Don't we know, Alta, already that what's conveyed by the last two is not captured by the present regulations?

PROFESSOR CHARO: What is conveyed by what last two?

PROFESSOR CAPRON: The full versus—

PROFESSOR CHARO: Oh, I wasn't even talking about, you mean full consent and general consent?

PROFESSOR CAPRON: Right.

PROFESSOR CHARO: Oh, I didn't even touch on those. No, I was only talking about administrative review and full review.

PROFESSOR CAPRON: I mean the whole notion of expedited, waived, or so forth.

PROFESSOR CHARO: Right. Those are separate from the concept of consent. I found full consent and general consent also to be confusing and nonintuitive ways of conveying what was being attempted to be conveyed. But I was focusing only in my kind of regulatory obsession over here on the regulatory language.

PROFESSOR CAPRON: Well, the consent language is in the regulations.

PROFESSOR CHARO: That's right. The word "consent" in the regulations does not track this distinction between full and general in any way.

PROFESSOR CAPRON: That's right. That was my point.

PROFESSOR CHARO: That is true as well, yes.

DR. SHAPIRO: Carol?

DR. GREIDER: I agree with you, Alta, that I think that what Zeke was trying to get at, back to the first two issues, wasn't very well fleshed out and we didn't discuss it a lot in the subcommittee. But I do think that there was something that he was trying to get at, which would be some sort of an additional looking at issues in terms of community and that sort of stuff that isn't in the current regs that I hope that when we fill in the boxes we will incorporate that and use some other language, with the idea being people haven't thought about community and, if we are going to bring that in, somebody has to determine whether this researcher has completely ignored a major issue and has decided that there's no implications of this protocol, and that needs to be reviewed by somebody.

PROFESSOR CHARO: My point, Carol, is simply that somewhere lost in the discussions that led to whatever information was being used to generate these boxes, somewhere lost in there was the degree to which some of these things are already handled with the regs, already require certain things, and knowing that will help us to identify where they need to be added to, changed, or, in some cases, certain things deleted. But at least we'll be working off of a regulatory framework that exists. When the rules get changed it will be virtue of amendment of those existing regs.

DR. SHAPIRO: I agree with that. If you go at it that way, you come up with words like "expedited" and "waiver" which are already defined and we could kidnap where appropriate and change where inappropriate. And so we'll need a different way to look at that. And that's a part of the homework that Tom gave may be helpful in that respect, Alta, or whoever provided those charts on the regulations, that really would be helpful.

PROFESSOR CAPRON: Did you mean kidnap or hijack? They're both Federal offenses, but one of them is worse than the other.

DR. SHAPIRO: I don't know which one I would choose then. But, in any case, perhaps we ought to come back to these issues tomorrow, and Tom has assigned some homework. And Kathi, maybe you, Eric, and I can get together to talk a little further about that right now.

ADJOURNMENT, DAY 1- Dr. Harold T. Shapiro

DR. SHAPIRO: And we can adjourn the meeting. Thank you very much.

Adjournment, 5:13 p.m.

DAY 2 CALL TO ORDER - 8:17 a.m.

WELCOME AND OVERVIEW OF AGENDA - Dr. Harold T. Shapiro

DR. SHAPIRO: I call today's meeting to order.

I'd just like to remind the Commissioners of the general scope of our agenda here today. We are going to spend our initial few minutes this morning revisiting rather briefly the issue of the proposed scope or nature of what this Commission might address itself to with respect to international research issues. We had some presentations on that yesterday. We've had some very brief discussions at previous meetings about that. And over the next little while we do have to define a task for ourselves in this area that's compelling and interesting to us. And I like us to begin that discussion. We don't have a lot of time to spend on that this morning. I would then like to return to the issue of the use of human biological materials which we discussed yesterday. A number of things I have on my mind there and other things which other members of the Commission might wish to address. We're then going to spend a good part of the morning looking at some cases in this area.

We do have two speakers who will be with us from the National Human Genome Research Institute and they'll be discussing a particular case, in fact a very interesting and fascinating case, and I think it will be helpful to us to listen and understand and try to think through what we would feel comfortable with in a case like that. Also, David has some cases which we might look at, and Steve I know provided Kathi with the material which formed the basis of a memo Kathi wrote, the material basis of issues that Steve brought forward. And I think it just might be very useful for us to consider these cases and go back and forth a little bit between how we want to sort of abstractly deal with these issues and sort of test these ideas out in the context of some particular cases. That will probably use up most of the time this morning, we'll just have to wait and see. We have some time reserved for that this afternoon if it still seems at that time that it's productive for us to continue conversations in this area.

And then, of course, we want to go to research involving persons with disorders affecting their decision making capacity, which is always a mouthful to say and I'm always never quite sure if I'm getting it out correctly. But in any case, we did have an interesting draft to review and a lot of issues there to be resolved also. And we will get to that as soon as we can. I know that it's always difficult to retain enough of us here as the afternoon wears on because of the imperatives of travel schedules, plane schedules, other kinds of commitments, so if we do have a capacity to get to the that particular report for which we have a draft earlier, we'll take advantage of that so we can go to it somewhat earlier and have as many of the Commissioners here as possible for as much of the discussion as we can.

In that context, Eric spoke to me yesterday, he has something that he would like to speak to us about regarding the Saks paper which some of us have seen. And we can describe that and Eric has some views on that and others may have also. We'll get that more generally distributed as soon as we can.

So that's the general nature of our discussion. We will adjourn no later than 5:15. We probably won't last that long, but, in any case, we will certainly go no later than that.

FURTHER DISCUSSION OF INTERNATIONAL RESEARCH ISSUES -

Dr. Harold T. Shapiro and Commissioners

DR. SHAPIRO: All right. So let's go to the first issue on the agenda, which is really left over from yesterday when we ran out of time, with respect to international issues. Let me turn to the Commissioners to see what ideas you have, what things you think might be an appropriate scope or nature of anything we might do in this area. There is of course a lot of other activity going on in this area. And as I announced yesterday, I've asked Alex to take some leadership here in helping mobilize our efforts in this area and I'm very grateful to him for agreeing. And to repeat what I said yesterday, any Commissioners who would like especially to work on that area, please let me know. We would be most anxious to accommodate you.

I have some ideas in this area, but I would like to hear from Commissioners also. Alex says he'll be all ears since he's got to listen and mobilize our agenda in this area. Let me get started here.

Oh, Bernie, I'm sorry, I didn't see your hand. Bernie?

DR. LO: I think this is a really important topic. My concern is that it's very, very broad and sort of nebulous.

And unlike the other things we've worked on where we had both a very clear focus and I think a clear audience that was interested in what we had to say, I'm a little concerned here about who are we going to be hoping will read our report and act on it. I guess personally I am not very enthusiastic about trying to work towards a revision of international codes for a lot of reasons, but, basically, I'm not sure people are going to pay much attention to them.

I do think it may be worth trying to identify what are going to be the hot issues regarding international research, particularly in an environment where I think we're going to be seeing more of it rather than less of it. I think we don't want to focus on specific issues, like these neonatal HIV prevention trials, but the whole notion of placebo controls and standard-of-care in other countries and how that effects the design of studies. I think that's going to keep coming up.

I guess my caveat is provided we think there's some assurance that what we say will not fall on deaf ears, I think we should try and identify what we think the pressing issues are or are likely to be and provide sort of an analysis, sort of an approach to it rather than trying to sort of make specific recommendations on how the Helsinki Declaration might need to be amended or whatever.

DR. SHAPIRO: Okay. I'm going to turn to David and to Arturo in just a moment, but I did neglect something right at the beginning I intended to do. We have a former colleague and guest with us this morning, Dr. Zeke Emanuel is here with us this morning primarily to discuss the issues regarding human biological materials. We will ask him to join our conversations at that time. That is to occur very briefly. So, welcome back.

DR. EMANUEL: Thank you.

DR. SHAPIRO: I just want to indicate to everybody that this is not an extra Commissioner or call-back Commissioner but a guest here this morning to help us with one of our discussions.

David?

DR. COX: I share some of the same concerns that Bernie just brought up. And so I asked myself from what perspective do I really want to address these issues. I guess in the process there's two perspectives, there are two things to look at. One is, are there general ethical principles with respect to research in international research that can apply across all different cultures and all different countries? That's the international code. It's not likely we're going to change it. It's a much more difficult question then, what are the principles that apply in American society and culture? In fact, we are the National Bioethics Advisory Commission.

So to look at those two different things because I believe that the utility of this investigation into the international things is going to basically be to inform us about how other cultures and views look at things other than the United States and it will have great utility for us addressing things with respect to the United States. In fact, it's not so much us giving pronouncements for the rest of the world as the rest of the world informing us. So that's what I mean about perspective.

On the other hand though, that's very parochial if it's just what can you do for us. And so I think at the same time we can say out of those things that are useful for our own deliberations with respect to types of research, what are the overriding issues that do cut across different cultures. And there are going to be some of those, but it's not going to be nearly as much as how do other people look at things that may differ from our viewpoint. And the AIDS AZT research is a classic example of that because it was an example of American viewpoints that differed with other people's viewpoints perhaps. So it's a perspective issue. It doesn't help with the exact things we're going to do, but it's the perspective that we're coming from.

DR. SHAPIRO: Arturo?

DR. BRITO: I agree with David that we do have a lot to learn from other cultures in looking at how they do research. But my understanding is that what we're going to be looking at is international trials, or we should be looking at is international trials that are U.S.-sponsored either by NIH or other entities in the U.S. and seeing how well the U.S. sponsorship of teams comply with even our basic codes.

There was a memo that the staff sent out to the Commission members and I have some points that I think are important. It particularly addressed the AZT trials. There's a line in there that the recent decision to cease the use of placebos in such trials render such an approach moot. I'm not convinced that all the trials have stopped at this point. And even if they have, even if they have, there's still some what allegedly would be inappropriate research has occurred

recently. I think this would be an opportunity to use this as a basis for how U.S.-sponsored trials can go awry.

I think that we've brought up before that there may be cultural differences, biological differences, etc. But it seems to me that we need to look at why the decisions were made to stop the placebo-controlled trials, what was the basis of that, and maybe use that in a positive end. And then there's also a line in there, "The Commission should consider addressing the issues in both developing and developed world." Well, that goes without saying. But what we're really emphasizing is that making sure that the criteria used for research in the developed world is also being applied in the developing world, particularly with any U.S.-sponsored or Western-sponsored trials. But, obviously, we're going to be addressing the U.S.-sponsored trials.

But I think there should be no distinction in how codes are upheld with either private or publicly-funded research.

So, in essence, I think this is an important topic we should address. I think that the HIV, the AZT trials should be used as a starting point just as an example, and that what we really need to do is also what we need to get from the international community is basically cultural differences and interests from there and how they may apply to U.S. sponsorship.

DR. SHAPIRO: Thank you. Alta?

PROFESSOR CHARO: Based on yesterday's presentation by Tom Puglisi and the comments from Bernard Dickens, it struck me that if we wanted to take a fairly narrow focus that builds directly off the AZT trials, we could say that what we would like to do is examine the actual practice of U.S. collaborative trials abroad with regard to four kinds of topics.

Given that we have the CFR already governing for many circumstances some of the procedural requirements that the foreign institution and foreign investigators have to meet in order to collaborate with the U.S. investigator, there are still substantive questions about the actual distributive justice questions—about subject selection, notions of vulnerability and potential exploitation in that local culture, and in the particular kind of risk-benefit balance that is permitted for the protocol overall as well as for the construction of the control group. Those are things that are not answered by the existing regulations which focus on the procedure for decisionmaking but not its content. And this is where the CIOMS guidelines are a beginning for the discussion. But we have yet to decide for ourselves if we'd like stronger guidance for U.S. IRBs about whether or not they should permit their own investigators to collaborate.

The second, which is in fact addressed by the regs but perhaps is subject to further discussion and even change, is in the area of the nature and quality and evidencing of informed consent. Because of the frequent problems with notions of personal autonomy, legal status of certain persons, particularly women, in many cultures, there is frequently a problem in the quality of the ability to obtain informed consent. And there is a U.S. requirement for a physical evidencing in the form of a signature or even an X. The signature actually becomes a problem in some cultures and we see many requests to waive that portion of the requirement. I suspect that many times it is being waived inappropriately in kind of a sotto voce way. And we could revisit what it is that we want in terms of both the nature of the consent and how it's evidenced to meet both our needs and those of the local culture.

The third would be what had been focused on yesterday in the questioning, which is the enforcement mechanism. Regardless of the actual authority that we have, what is the ability on the ground to get cooperation from foreign institutions to investigate or to have site visits and is it sufficient, and how can we improve that kind of cooperation, which is going to be very much about local culture and about U.S. relations with that culture. And it won't necessarily be that it's developing countries that are the problem; I suspect that it will be our colleagues in Europe who have got well-developed systems of their own who may turn out to be the least interested in having the U.S. come in and play enforcer.

And the last, which Tom was emphasizing in his responses yesterday, is probably the most difficult because we haven't done a really bang-up job yet in the U.S., and that's the problem of educating investigators into the culture of research ethics that ought to apply in the course of a protocol. Since that's really the most important protection for human subjects or human participants in research, to the extent that we've figured out how to educate our own PI's, some thought about how one might try to quickly transfer that education to our foreign counterparts as part of a collaborative protocol would be interesting. And that would be an agenda just for the narrow how do we do U.S. trials

abroad kind of approach.

DR. SHAPIRO: Thank you. Larry?

DR. MIIKE: I guess this is more for Alex as he does his investigation. Expanding on David Cox's comments, I would be interested to see what other developed nations see as deficient in our system. It is sort of the way of what Alta was talking about, is that if the criticism is that we don't, say, have universal health care, it may back us up into the issue about compensation for research subjects. But what sort of a mirror back at us about what do people in other developed countries see as deficiencies in the way that we do things.

DR. SHAPIRO: Thank you. Yes, Laurie?

MS. FLYNN: I would just want to reinforce the last two points that Alta made. I think it's critically important that we recognize the culturally-relevant context in which this research goes on, and that if we have concerns, the ability to have site visits, and I understand the negotiations that would be involved. But I think it would be important in terms establishing kind of relationships that would lead to greater assurance that ethical standards are being met.

And secondly, I think it goes without saying but perhaps needs to be said regularly that the work that needs to be done before we can think of anything else is upgrading and enriching the education for investigators, the understanding of the dynamic of ethics and their ability to participate much more fully than I think some have. And that's an issue that we have to address here in this country I think much more strongly than we have before we can imagine exporting it effectively. So I just want us to remember with some humility how far we have to go here.

DR. SHAPIRO: Thank you.

Trish?

MS. BACKLAR: I just would like us to remember to be very, very sensitive to the colonial aspects of this discussion and that's all.

DR. SHAPIRO: Alta?

PROFESSOR CHARO: It is, depending on how it is structured, but if it does focus though on U.S. collaborative research, not even necessarily on U.S.-sponsored research, but U.S. collaborative research, U.S. investigator and foreign counterpart, we can direct the comments very much to the circumstances under which our own researchers are permitted to collaborate. Not a matter of telling other countries how to do their own research, but a matter of telling our own investigators whether or not they're allowed to participate in it. I think that avoids some of those problems.

DR. SHAPIRO: Thank you. Any further comments from Commissioners on this?

Tom?

DR. MURRAY: I think it has come up at least indirectly, but I wouldn't want us to loose sight of the primary issue that in the past year or so has brought this to the fore, and that is when you're looking at lesser developed countries that do not have the resources and the infrastructure or the standards of care that we have in the developed world, and when it is proposed to do an investigation, one or more of which treatment conditions would be a standard-of-care less than that would be provided here. I just think we need to address that. It's been called a placebo group. It need not be a placebo group; it could be an older form of care that's a lot cheaper. But the key thing is when you're—and the bite of moral criticism that I recall in the debate we've had in the U.S. recently has been to remind us that we should never expose human subjects to a standard of treatment less than that which they should otherwise receive. But that has not been contextualized in an appropriate way. And I've heard some very good arguments on both sides. This is the sort of issue I think it would be worth our delving into more.

DR. SHAPIRO: Thank you. Other comments?

Alex?

PROFESSOR CAPRON: I would like to hear in the weeks following this meeting any further ideas people have about issues of that type. I think Bernie began the discussion by saying that the placebo control, and as Tom has said, is a slightly broader question than just the placebo control. But the design of experiments, to what extent are there

other "hot issues" that are not procedural issues of the type that we've spent most of the time on, which I think we have to figure out how to get a handle on those, and I found this a very helpful discussion, but if there are other issues of that sort. And we can ask, as I think has been implicit in several of the comments, are there issues we think that exist domestically for which looking abroad becomes a way of looking at them and almost diffusing them a little bit. It's as though we were talking about a hypothetical, and then turning back and saying are there ways that, after we look at them abroad, that we ought to actually be concerned domestically and what effect would they have on the U.S. regulations as well.

I'd be happy to get any of those. And I will try sending an outline in the next week or so of these and discuss with staff how we might go about on a continuing basis in the next few meetings having input that will help us to pursue different avenues.

DR. SHAPIRO: If I could just say a word about this, as we wind up this small part of our agenda today. Picking up on some comments I think that some of the staff made and Alex made yesterday. I think the issue that Tom points to or issues like that are very important to address in some way. But, on the other hand, I'm hoping that as we form our agenda here that it's a little broader in context. That is, my own sense of it is it shouldn't be just collaborative research we do with less developed societies. If you looked at the NIH data yesterday, in fact, most of it is not there. Most of it is in the U.K., and Canada, and Australia, and so on, which are hardly less developed places. And so we're going to have to have a perspective that includes, in my view, something beyond this special case, which is important enough, I quite agree with what Tom said and he raised a lot of issues in this last year.

I also think that we need to at least consider going beyond Federally-funded projects. That is an issue that Alex raised yesterday, if I recall. That is, there's an awful lot of U.S.-sponsored research in this area going on abroad that, first of all, it doesn't go through NIH or HHS, it goes through some other government agencies, but there's an awful lot of private research. Certain kinds of trials are typically held abroad. And I think we might want to understand what the scope of that is, what the nature of that is, why that is, and whether that raises or doesn't raise any particular problem.

So I'm hoping that as we begin to focus down on the agenda we can have a sense of this dealing not only with the key issues, one of which Tom has raised, which are very important, but get ourselves informed about this broader concept and see whether that raises any issues for us. Until we know more about it, it's hard to say. I don't have any perspective one way or another, but I hope we can take a broader look at it. Eric?

DR. MESLIN: Just very briefly for the Commission's information. This subject is not limited to what report we might write, but also the way in which the Commission itself is being perceived and looked to internationally. Our reports will become part of the international dialogue on bioethics which is increasing apace. You heard from Dr. Alexander yesterday about one of his roles as the U.S. observer to the Council of Europe, others have played a similar role at UNESCO meetings. And there is an increasing interest amongst the world's national bioethics commissions of the way in which they can have a common dialogue on issues of mutual interest.

So whatever we come up with will serve an educative function iteratively, both they learning about how the U.S. National Bioethics Advisory Commission functions and speaks to these issues, and how we can learn from those other commissions. Several meetings ago Dr. Shapiro mentioned that in November there is a planned second summit of the International Association of Bioethics to take place at this point in Japan. And that may be an opportunity for whatever the agenda we are putting together, which will form the basis of our report, to be raised as our perspective. This is something that I think the Commission needs to keep in mind.

DR. SHAPIRO: Thank you very much. Any other comments on this issue before we move on to the next item on the agenda?

FURTHER DISCUSSION OF HUMAN BIOLOGICAL MATERIALS REPORT -

Dr. Harold Shapiro, Dr. Thomas Murray, Dr. Kathi Hanna, and Commissioners

DR. SHAPIRO: Thank you very much. And let me thank Alex once again for agreeing to take leadership on this issue.

Well, we had a rather long discussion yesterday including a number of presentations in the general area of the

use of human biological materials. I think, at least my own sense of our conversation, is we came to some kind of quasi resolution yesterday that was, in fact, really quite productive. I'll wait and look at the transcript to make sure that I haven't sort of selectively listened to what was going on. But it was my sense that we really had taken our discussion a step forward.

I wanted to say two things which I think, at least for me, helped us take the next step forward. One is, although I think that our focus on what we have called the boxes, and that means a lot of different things, has been extremely helpful to us in formulating our ideas and so on. I think finally it's come to really get in the way of finding a resolution. I'm going to propose that, in fact, as we go ahead in our discussion, and I've discussed this, as I mentioned before, informally with a number of Commissioners after our meeting, that we really try to look to frame our discussion around something which might be a decision-tree approach or a flow-diagram approach, depending on how you call these. I think it just leaves us a lot more flexibility. At least as I visualize it right now, if you had a "decision tree" approach to trying to partition all these various characteristics, at the bottom of the tree would be the protections that NBAC suggests in each individual cases. I think, in fact, that will help us work our way through a number of the issues that we discussed yesterday.

I don't know if Carol managed to put them on overheads, but I mentioned this to Carol last night at dinner and she came in this morning with a decision tree worked out. So she will present that in just a moment just to give you an idea of how that might work and see if we think that's helpful or not.

Also this morning, and I think you all have your place, Alex took the initiative to listen carefully to what we've been discussing with regard to definitions and came up with some alternative definitions. This was the last page of Chapter 5. I've only taken a quick look at this and not carefully yet, but it does seem to reflect from my quick look what —

PROFESSOR CAPRON: One major typo.

DR. SHAPIRO: Well, I didn't see the typo.

PROFESSOR CAPRON: Under "unidentifiable materials," after the word "which" should be the word "no."

DR. SHAPIRO: Yes, that's right. And if we have a chance, we should also perhaps revisit this at least very briefly. But it does seem to me to summarize really rather nicely the nature of the discussion we had yesterday.

PROFESSOR CAPRON: That reminds me. I called on a student once and she gave a very elaborate answer to the question. I looked a little skeptical, and she said, "or exactly the opposite."

DR. SHAPIRO: All right. So I think that, in fact, our discussion moved ahead quite substantially.

But I think it might be interesting to just see what Carol came up with overnight just as an illustration of the kind of way we might sketch it out. I don't know that Carol wants us to take it all just exactly as it is. Alta had also taken a shot at some decision trees yesterday which I saw which haven't looked at carefully. You may want to say something about that as well, Alta. And as I said, after this, as soon as we see this and see if that sort of helps people think things through, if that's useful, we will, of course, work it out in greater detail, but then we will turn to cases this morning.

DR. SHAPIRO: Carol?

DR. COX: Carol, excuse me. Can I just say that I really like the revised wording in these definitions because I think it's exactly what we talked about yesterday and it clarifies some ambiguities that were, in my view, in the previous wording. So I really like this very much.

DR. SHAPIRO: One of the other conventions, I would say, that these seem to incorporate, these definitions, is we decided, or at least it was suggested, I think it was, I've forgotten, Alta's suggestion, somebody's suggestion, that in our discussion we reserve the word "samples" for what it is investigators have and use and we stop using it for many other ways it could be used in this context. I think that actually helps in the discussion and it helps clarify our thinking and our writing in this area, and that's reflected in these definitions here, at least as I understand it. So, Carol?

DR. GREIDER: I gave my overheads to Henrietta to make copies for everyone and until she's back retrieving those from the photocopy machine, I'd like to just make one comment about the definitions that were passed out just in

terms of the language, although I agree with most of what is written in these definitions. The term "unidentifiable materials" seems needlessly long to me. Can't we just call it "unidentified" and "identified" in the top two definitions?

DR. DUMAS: No. It makes a difference I think.

DR. CASSELL: Unidentified is the state, unidentifiable is the process.

DR. GREIDER: But in the repository, the material is, in fact, unidentified.

DR. DUMAS: That might be true, and it might also be unidentifiable or it could be identifiable.

DR. GREIDER: All I'm talking about is the first two definitions. In the repository there is either identified material or unidentified material in the first two definitions. It just seems overly cumbersome to say unidentifiable material when, in fact, it's sitting without any, nobody knows anything about it. It is, in fact, unidentified.

DR. SHAPIRO: Is unidentified you think it cannot be identified?

DR. GREIDER: If that's the definition that we're making for those first two classes of material that are sitting in repositories.

PROFESSOR CHARO: Carol, besides the extra syllable, what is it that's cumbersome, so I appreciate what you're trying to get at?

DR. GREIDER: I'm just trying to simplify the language because I found, when all the previous discussions that we had about identified, anonymized, anonymous, all of these sorts of things, there are very subtle meanings that are tacked onto suffixes and prefixes, like identified anonymized. And I'm just trying to simplify it so that you get to exactly what you mean in the simplest possible words so that nobody can read anything additional into what you might be meaning.

DR. MURRAY: Simpler is better. But I think calling them unidentified leaves open the possibility that somebody could then go in and identify it. This is an unidentified lost object. Well, we've now figure out who it belongs to. Unidentifiable indicates that even if you made an effort, your efforts were not likely to be fruitful. So I think actually there is a denotative difference.

PROFESSOR CAPRON: Why don't we all think about Carol's suggestion? It's worth playing through the alternative.

DR. GREIDER: And maybe we can discuss the actual language that's going to go in there a little bit more later on.

PROFESSOR CAPRON: The purpose of putting something on paper was to have something to shoot at. It's hard when we have these generalized oral discussions and then we don't know where we are.

DR. GREIDER: So from our discussion yesterday, we had discussed—this is now just for the stored material, not for the future material—we had discussed that there are two types. And here I've used the term "unidentified," and we can have the discussion about how we're going to call that, "unidentified" and "identified." That this is how the material sits in the repositories.

The unidentified wouldn't go any further. And into this box here we would put what the protections would be that we would want to give to this particular kind of sample.

Then there is the identified sample. And from these identified samples we broke it down and said there are three ways that you can treat this. One is that it can be coded so that it is not traceable, and, again, I'm using the old language, we can change the language in this box but I think that we'll have to agree on the actual meanings. The other is coded so that it is traceable in some manner. And this is going to have other possibilities attached to it. And then the third possibility is that it is actually identified.

So the one that breaks down then is coded so that it's traceable in some manner. And I've given this molecular biologist's "wedgie," we call this little thing, to indicate that there's a continuum of different kinds of protections that you might give to this material that is coded. I've only written down two of them along this continuum. We can discuss various other kinds of protections that might go in. But the two that we talked about most in the subcommittee are that it

would be encrypted in some manner so that you could have feed forward information coming from the physician, say, to the researcher, but the researcher cannot go back. And the other would be that it would be encrypted in some manner so that you would have feed forward and walk back capability. So that's why this arrow is pointing in both directions. Maybe we can discuss this.

And then I've also done this very much an analogous one for the future samples. And I can put that up afterwards if we want to discuss it.

I'll let Harold handle the questions.

DR. SHAPIRO: Yes, Bernie, Alex.

DR. LO: Carol, I like this very much. Visually, it helps me to understand it better than having just a list of definitions. I'm trying to make sure, I know the terms are not exactly the same, I want to make sure the boxes are the same. So under what you're calling "identified stored material" which the sheet of definitions we have calls "identifiable," it seems to me that the farthest right hand box on the next level down of the samples, what you're calling "identified" is meant to be what the sheet calls "identifiable." So they're readily directly linked to a person.

DR. GREIDER: Right.

DR. LO: Okay. Then the middle box, the coded traceable, what we're calling "coded samples" and what you're doing is introducing a further branching of that category.

DR. GREIDER: Correct.

DR. LO: Which helps me because I think there are important distinctions in that category that the definition here doesn't quite make stand out.

And then the box on the left, the "coded but not traceable," is that meant to be the same as the "unlinked" samples?

DR. GREIDER: Yes.

DR. LO: Okay.

DR. GREIDER: And we could change the language in here. It's just that Alex and I didn't get together on the definitions.

PROFESSOR CHARO: Carol, a question also about the decision tree. "Coded not traceable" is what we had been discussing as the situation in which a code was attached so that information could flow forward on a collective level. What is the point of "coded not traceable" in that left-hand box if in the middle section you've got a version where you have encrypted feed forward?

DR. GREIDER: Right. So these two I think are actually distinct and it depends on how you do the coding. You could come up with a three random number generator where the middle key is thrown away and so that nobody can ever go back and get any information. I think that is distinct from there being some sort of a code and whether encrypted and who knows the code is debatable. But if there is a code and you can go back, there is a distinction between those two cases.

DR. SHAPIRO: We have a lot of people who want to speak. Alex?

PROFESSOR CAPRON: What I had hoped we would be moving to as we get to a flow diagram would be what this will permit, which is the next step of asking what protections and then you have yes/noes that come out of this. And it may well be, to carry that thinking through, that rather than spinning out further and further definitions as such, we ask the question about things which are coded in a way that there is a link between the code on the sample, you don't know looking at this whose it is but that code is attached to some means. The question would then be, can the laboratory, the repository, or the information system provide further information to the researcher as it is accumulated about the subject? If the answer to that is yes, then we're moving into what you call the "encrypted feed forward," and there would then be certain questions.

Because each of these categories is potentially different only if we think that a risk arises there. And the only

thing that I see immediately that I don't see up here was the point that David made yesterday, and that is—and I think Alta gave him part of the example or someone else gave him part of the example that led to this—when we talk about something "encrypted feed-forward," we also have to think about the fact that what that means is that the repository knows how to link its material with its identifiers on it to the sample. It is just that the person who has the sample doesn't know how to link the other way. So if the person who has the sample comes up with research results which they attach to a research sample which they supposedly can never know who it is, and the repository, the person who is running the repository has that information, that person can make a link. And so it's not to say that we shouldn't allow that to happen, it's just that raises a concern which I hope that this division doesn't obscure.

Because by looking at the feed-forward side, it doesn't recognize that there is, in effect, a feed back way where the repository can, you might call it a pull back instead of a feed-back or walk. It's not a matter of walking back, it's a matter of my, on the repository end, looking over at the data and saying, "Oh, well, I know who that is even though you don't know who that is, Mr. Researcher." Anyway.

DR. GREIDER: Can I respond to that?

DR. SHAPIRO: Yes.

DR. GREIDER: If I can just give my interpretation of the history of where we went with the genetics subcommittee. Zeke had started out with this very full matrix that we were discussing all of the different boxes. And then as we started thinking about what protections we would fill in, we started eliminating a number of the categories because the protections were the same in the individual categories. And then what we brought to the full Commission was a much smaller matrix than we had initially started with. And that caused all kinds of confusion on the Commission because people didn't understand why we had eliminated some categories that one would logically think of.

So I've now come back around to thinking we should have a framework or a flow diagram that encompasses all of the different possibilities and, even if the protections are the same that we're going to fill into these different boxes, we should leave them there because other people looking at what we did will then be able to understand from a logical point how we got there. And so I don't want to run into the same problem that we ran into going from the genetics subcommittee to the full Commission going from the full Commission to the world not being able to see where our logic was.

PROFESSOR CAPRON: I have no argument with that. Thank you.

DR. SHAPIRO: Let me just say I have a lot of people who want to speak. Let me tell you what the list is before I make a remark. David, Rhetaugh, Steve, and Larry, those are the people I have on my list. Zeke, also. Zeke, in fact, was the next one on the list.

But I do want the Commissioners to understand this is not a proposed final issue. This is just to show you how such a scheme might work our way through. Of course, at the bottom of all these trees or diagrams would be a set of protections, which has been the key issue. So that would have to be worked out and maybe it would be this scheme or maybe it would be something like it. We ought not to get too focused on the exact nature of this yet but just whether we like that way of thinking about it. Zeke?

DR. EMANUEL: I just wanted to make two brief points. First, to complicate things, there are two elements of materials here usually, and those of you who do research a little more with this stuff than I do correct me. One is the actual biological material, the slide, the sample. The other is the clinical material which is distinct from the biological material. It is either, in case of a clinical sample, the patient's clinical history, whether they relapsed, or, in the case of research studies like the Physicians' Health Study or the Nurses' Health Study, the ongoing data collection that is being updated all the time.

It seems usually, again, you have a one-time sample, the biological sample, and then the issue is the continuous clinical update. And so there's two kinds of materials that need to be thought about here. It's not that you usually have a continuous update of the biological material, but of clinical information on that.

The second thing I would like to say, now having talked to a variety of groups, I think the emphasis, the real issue for clinicians out there and researchers out there are the bottom two over, "coded so traceable." That's the real divide. The encrypted feed forward so you cannot walk backwards, not only can't the researcher walk backwards, but

even if the repository wants to pull information back, it can't get the result back. I don't think that's right Alex.

PROFESSOR CAPRON: That was David's example.

DR. EMANUEL: Well, I think that falls into the "encrypted feed-forward and walk-back." If anyone can get that, attach the name to the result, that's walking back. If no one can do it, then that's feed-forward only. That's the way I had understood those kind of boxes.

It seems to me the real emphasis from the practical standpoint, where are the majority of research studies, where is the majority of the problem are in those two boxes. I would just urge the Commission to really—that's where the money is, as it were.

DR. SHAPIRO: David?

DR. COX: Actually, I'd like to follow up on exactly where Zeke's going and attempt to be as clear as possible here. With the present regulations and speaking as a researcher, from the perspective of a researcher, that a desire to use tissues but at the same time have protections for human subjects, the way the regulations are written now, if we're in the box of "coded but not traceable" that's okay with the present regs. And that's how researchers have been doing business for a while.

But even from the researcher's point of view, although the researcher can get the tissues, it's not scientifically the best. And the reason why it's not scientifically the best is because it gets rid of other types of information that are very valuable scientifically. And it's this clinical and extra information, not necessarily the clinical, but additional information of which clinical information can be one type that goes along with the sample.

And so as a researcher, one says how can we maintain the protection for the subjects and at the same time get this extra information. And there's only one way it can happen. It doesn't work if the repository scrambles all the information. Somebody in the repository has to be able to keep track of what information goes with what sample. There has to be some way of doing that. And that's why the coded and traceable is important because, as a researcher, if it's not traceable, then I lose information. And so speaking as a researcher then, I want the repository some way to feed me additional information and at the same time being protective of the human subjects.

Now not speaking as a researcher, but now speaking as a research participant or a patient is that the researcher may not care if that information can't go back to me but I care if can come back to me because if there's no way it can come back to me, I don't get any possibility of direct utility out of it. So it depends on whose perspective you're looking at in terms of if it makes a difference of whether it's going forward or back. And I would say as a research subject that if it's my protections that are being looked at, then it is not only discrimination against my material, but it's also the utility to me in terms of the use of it. So the point I'm making here is not looking at it just from the point of view of the researcher, of which I am one, but trying to look at it from the point of view of the research subject, too.

And so right now it is absolutely true that the research community and the public are one with the idea that making things not traceable seems like a high cost to pay for protection. And is there some way, and this is the punch line, is there some way that we can keep things traceable and still protect people? Having said that, once they're traceable, then what are the protections?

So, to me, the issue is whether they're traceable or whether they're not traceable at the repository level, that's why I like this conceptualization so much, then Zeke, after the fact, if they're traceable by the repository, then we start talking about what type of information, how much, and when it goes forward or back. I think a rigid statement which is nothing will ever go back is not practical. It's practical from a researcher's point of view, but I don't think it considers all the possibilities from everybody else's point of view.

DR. EMANUEL: Can I just respond with two things. And I may be completely out there, but, as I understand it, the real issue and the real potential harm is when the result goes with the name. That's the key issue of traceability. Does result Q, BRCA1, yes or no, go with—can someone link those two pieces of information. Because if they can't link them, then they are not traceable. Because the key issue isn't did you know that this sample was in that group. That's not the issue I think. The real harms come with the result being linked to the name. And that I think has to be where we keep focusing on.

The second thing I would suggest to the last comment, David, is, again, remember what the person from the

National Breast Cancer Coalition said. They are willing to give up that traceability for more research. So you keep telling me what you think the research subjects believe, that they want that information back to them. At least one person who testified to us doesn't agree with that. It seems to me what we need to do is give researchers and subjects the choice, which box do they want to be in?

DR. SHAPIRO: We have a lot of people who want to speak. So let's please have some discipline in our mutual selves here.

DR. SHAPIRO: Rhetaugh, you're next.

DR. DUMAS: It's very interesting because I think people are speaking to different aspects. I want to go back to the diagram and change my mind, Carol, about the not identified and identified samples. Because if they're stored, I agree with you, they are either identified or not identified. And what happens after that is a different story. So I'm with you and it helped a lot to see it up there.

Now with the identified material, you have "coded not traceable," "coded so traceable." It seems the other category would be "not coded."

DR. GREIDER: That's "identified."

DR. DUMAS: It's already identified.

DR. GREIDER: That is the other category.

DR. DUMAS: Yes. It's already identified. And if you're going to have three categories of identified material, this might be nitpicking —

DR. GREIDER: Oh, you're talking about the language?

DR. DUMAS: I'm talking about the logic of the diagram. You have "identified," "coded traceable," "coded not traceable" and the next one would be "not coded."

DR. GREIDER: That's what it is. That's what I meant by the identified goes to "identified." It's not coded, it's —

DR. DUMAS: It's not coded. Okay. What I don't understand is the difference between "coded not traceable" and "encrypted feed forward."

DR. GREIDER: Because you could have a mechanism of encoding something where nobody can ever go back. Imagine three different computer programs generating random numbers and you throw away the middle one. So the researcher can't go back and the repository can't go back.

DR. DUMAS: Is that not true of the "coded not traceable"?

DR. GREIDER: That's what the "coded not traceable" is, is that nobody can ever go anywhere with that information. It's impossible.

DR. DUMAS: Okay. I understand now. I got it. Your "coded so traceable" can be changed so that it becomes essentially what you have —

DR. GREIDER: And that's "encrypted feed forward" or "encrypted feed-forward and walk-back."

DR. DUMAS: All right. I got it. Now one of the things that I think we have to make sure that we do, and Zeke reminded me of this, is to be able to separate out how we think about the material from how we think about the information, both the information about the subjects and the results, too. I think we can get confused there how we think about the materials, the samples, and then how we think about all of the information that would be associated with that.

DR. GREIDER: One of the questions is in a lot of these categories there is no information associated with it. That was the point. So the "not identified" and the "coded not traceable," there is no information.

DR. DUMAS: In the "not identified" there's no information about a priority —

DR. GREIDER: The information comes in the box that starts off "coded so traceable" and "identified." Those

are the only two boxes where information becomes an issue and the boxes below them.

DR. DUMAS: Okay. And then what I'm saying is that how you handle the material and how you handle the information needs to be distinct.

DR. SHAPIRO: I have really four other members of the Commission who want to speak, then we're going to end this part of our discussion. We can rejoin it later in the day. They are Steve, then Larry, Tom, and Alta. So, Steve?

MR. HOLTZMAN: A couple of different points. One, as we engaged the language of other statements just for the staff to think about. In our nomenclature here of "not identified," something in a repository could be not identified because it never had personal information ever associated with it or that personal information was irrevocably removed. And that sometimes is how those statements use the latter as "anonymized." Sometimes they mean it is removed for the purposes of the study. So we should just be clear about that.

The second point goes to something Zeke was saying and leads to a third point, is I think we need to be clear about information, whether we're talking about information which is the paradigmatic personal identifier or information sufficient to identify the person. And I put that together as distinct from clinical and biochemical information associated with the sample. Whatever one means about not identified or no information, etc., it is the very, very rare study that is interested in just a hunk of meat with no clinical information associated with it. All right?

The third, and this is not meant to be more complex but it really struck me as we were talking here —

In other words, the results of the research can be hooked up with the individual from whom the sample is taken. So, it may be hard to do at your place. But what I found myself doing—in the identified bucket on the right was saying, "Well, now, it goes out to an investigator. It either is or is not provided with personal identifiers." Those were the two buckets that were really important. Now, again, first of all, identifier could be name; it could be sufficient information to point to the individual. The same is taken from three people who live on thus-and-such block, etc. If it is not provided with personal identifiers, then it is either possible to link your results to the person, or it's not. Okay? And this kind of ties — Alex made the assumption that it was possible to get feed forward information, than by definition. You also had to be able to get back to the person, and that is one of the things we're asking. So, if I find myself saying, it's either provided with personal identification information, or it's not. If it's not, you either can rehook it to the individual, or you can't. And within the bucket of you can't rehook it to the individual, you either have this snapshot of clinical information you get today, and that's it; or you can get a forward flow of information that's clinical, but not hooking you back to the individual. So, and I can redraw this and give it as a break. But I think that we may be confusing ourselves a little bit with the traceability, because the traceability we were interested in the feed-forward is flow of clinical information, but not anything that would be personal information.

DR. SHAPIRO: That's helpful if you can write it down. That's helpful. We can look at it, and think about it carefully. Let's go to Larry next.

DR. MIIKE: Clearly, the game is in the two right extremes — identified and an encrypted, feed-forward, walk-back. I, for the life of me, I don't understand the difference. They seem to be basically the same, except there is the repository person that is keeping the name. I don't know what you mean by "walk back." If it means that a person can get any access to anything over there. So — and even if we are in the identified stage, I don't think we're envisioning any research or being able to go and call the patient up and say, "Let me see your records, etc." So, to me the only difference between the identified and the feed-forward walk-back, is that there is another filter in there somewhere, which is the repository person saying, "I'm not going to give you the name." So, it depends on what we mean by the extent of the walk-back, how current that update is. So, I think we're getting already into what safeguards. So, to me the only difference between those two is that the repository filter of the safeguard between the two. This brings me back again to some of the issues that we had talked before in the subcommittee meetings, which is that, from my personal side, I would want the same protection for the feet forward and walk back, as it is for the identified. As long as they are fooling around with my information, at my individual level, I want the same protection. What other researcher has my personal name on it?

DR. SHAPIRO: I think a lot of these trees are going to end up with similar, or sometimes the same, protections. Let me go next to Tom.

DR. MURRAY: That feeds nicely into my next point. We began with boxes. Was it a millennium ago? It

was a while ago, we started out with those other boxes, as a visual metaphor for what we were trying to do. This presents essentially the same information in a different visual metaphor. We were actually—I think we had worked ourselves into a box a bit, using the boxes. So this gets us out of it, set a pathway now, a walkway. I could have let that one go. The point I want to fix on is what I think Larry ended with, and, that is, this is just an effort to capture conceptually the major options. Okay? We could actually make a much more elaborate set of paths. There is no question about that. The key issue is: Does this capture the main sort of choice points in deciding from the options? We have yet to decide what we would do in terms of protecting patients, or sources of human biological materials. Some of those, it may turn out, will do exactly the same thing, or two different ones. But what I'd like us to do is say, okay, this scheme is good enough for us to work with. Let's start talking about what protections go in each of these kinds of cases. If we decide that it fails to capture some important distinction, we can go back and we can refine it. But I would really like to see us, after we have the next talk, begin to work with this and talk concretely about policies and protection.

DR. SHAPIRO: Thank you — Alta.

PROFESSOR CHARO: Two points. One is that I find this particular schematic close, but not quite yet for me, as clear as I need to understand the scenarios at all moments, and I look forward to working away on this. The box called "coded, not traceable" still confuses me, because it seems to me this is about "not possible to go back or forward on an individualized level," at which point, I don't understand what the code is there for. It looks to me like it's simply uncoded or unlinked. And, at most, the repository has recorded which hundred people materials have been sampled.

DR. GREIDER: But remember our distinction that we are distinguishing between how it exists in a repository. So, the point is that it exists in the repository as identified.

PROFESSOR CHARO: Which you have already indicated above.

DR. GREIDER: We have indicated above, but we have then removed that information, so it has to be distinct from the not identified, because if it exists in a different state in the repository...

PROFESSOR CHARO: This we can work through on paper over time, but this particular discussion led me to wonder if it would go more to the heart of the matter, if instead of focusing on the mechanisms, codes, encryptions, etc., what we did was have the scenario flowcharts flow—be identified, basically, in terms of information flow. So, we have identified materials. There will be a category of samples that are provided to researchers, in which there is no ability on an individualized level to go back or forward. Whether it's due to codes, or encryptions, or whatever, you can't go back or forward. There will be a second category which you can go forward only, and a third category on which you can go forward and back. And by focusing not on the mechanisms, but on the information flow, we might be able to get closer to the set of concerns that we have, which is "How does the information flow relate to the outer parameters of risk and benefit to the people whose stuff is being used?" Which leads to the second, and this will be brief, because I know we're closing. When Zeke was suggesting to the Commission members that the only significant kinds of harms that we need to be concerned about are those that are associated with identifying a particular person, and linking that person to a particular sample, I found myself disagreeing, because I have been involved with several situations now, where collections of people have been identified as a group for whom there is a risk that they, in fact, have some characteristic. And the question that has been raised is: How does one approach members of that group to ask whether they'd like to be further tested to see whether or not they indeed have this characteristic? In some cases, it was paternity issues; other cases, it was disease carrier. And that's because there has been an investigation that revealed something about a high frequency of a phenomenon in a collective group. And the anxiety that can be engendered by just being asked whether or not you want to be further investigated is real and I'd like us to keep in mind that that's something to consider as we look through the risks and benefits of information flow back to people, even when it's not yet been linked.

HUMAN BIOLOGICAL MATERIALS, INTRODUCTION OF SPEAKERS - Dr. Harold T. Shapiro

DR. SHAPIRO: Okay. We're going to have to really end this part of our discussion. I know there is a number of others who want to speak, Alex, and so on. But I really — if you could hold your questions, we'll be coming back to this. This is not the end of our discussion today. But we do have some guests here, and they have been waiting, and I would like to turn to them, so that they can present their material to us. Lisa Brooks and Mark Guyer are both here, and I want to welcome them. Please come forward. Lisa Brooks is a Program Officer, the Genetic Variation Program, the Genomic Informatics Program; and Mark Guyer is currently Associate Director of the Scientific Coordination of the National Genome Research Institution. We are very grateful for them both coming here today. They are going to talk to

us about plans to develop a resource for discovering human genetic variations, with special emphasis on — and I'm going to test which one of the Commissioners understands this—single nucleotide polymorphisms. You can all write me about those later. Welcome, it's very nice to have you here. Thank you very much for taking the time to come. We appreciate it.

DR. BROOKS: You should have two handouts. One is the research —

DR. SHAPIRO: Is there no chair over there for you?

DR. BROOKS: I'm going to be standing by the overheads. One is a resources for finding human genetic variation, which is what my brief talk is an outline of, and the other one is the consent form that we're using. I'd also like to introduce Diane Wagner from CDC. We've been working with them about the use of this resource.

DR. SHAPIRO: Just hold on a second. Let's be sure that everyone should have a copy in their place. It was passed out this morning. If someone doesn't have a copy, maybe you—Trish, you don't have a copy? Let me see if I can find another copy. Anyone else? All right. We're all set. Thank you very much.

A RESOURCE FOR STUDYING HUMAN GENETIC VARIATION - Dr. Lisa Brooks and Dr. Mark Guyer,

National Human Genome Research Institute (HGRI)

DR. BROOKS: Okay. We were asked to present a case study. So, we are going to call on the box, on the top left, the nonidentifiable case. And this is arising—it's coming from the context of trying to map the genetic basis for various diseases—that the methods for finding the genetic basis for diseases that are caused by single genes are fairly straightforward. So, that's something that's happening now, has happened in the past. The methods are fairly clear for how to do that, and current genetic maps are sort of more or less adequate. But it's turning out that many diseases of interest, many common diseases—heart disease, cancers, asthma, psychiatric diseases—are called complex traits. They are effected by multiple genes, and they are also effected by environmental influences. And to find the genetic basis for these diseases is really a much more complicated process. In order to do this you really need much denser map, in order to find those things which do contribute to these traits. So, it's turning out that there is now new technology. What's driving this now is there is new technology, in order to find what are called single nucleotide polymorphism (SNPs). You have may have heard SNPs on chips. Well, that's what we're getting towards here. These are single places in the DNA sequence where there is a variance. For most individuals in the population, for example, they have an A, where some individuals may have a C. So, there are single point changes in the DNA sequence. And new technologies are coming out that are making these much easier to find. It's important to recognize that the genetic differences we're talking about are—most individuals, if you compare two chromosomes — or most individuals are about 99.9 percent the same. We are the same species. We do things pretty much the same, but about in one in a thousand cases there are differences. For the single nucleotide polymorphisms, the SNPs we're talking about, there is a minimum of 6 million in the human genome; maybe as many as 30 million, or even more. There are lots of these differences, so that we're aiming to have a map with at least 100,000 SNPs, which will enable the mapping of these complex traits much better. Now, of these single nucleotide polymorphisms, there are sort of two types to keep in mind — those that actually cause a functional difference; those that are actually the variants that cause or contribute to some disease. And, of course, there is a lot of interest in this in finding the actual genetic basis for the disease; drug companies, who are, of course, interest as well as researchers. But even those variances—and most of the variants are not going to have a direct functional effect, but the rest of those variants are very useful for mapping the ones that actually do have a functional difference. NIH now has a Request for Applications out. This is joined by 18 institutes. There is very widespread interest at NIH in finding these—these points of variations, these SNPs. Under two points to this RFA: one is to actually find SNPs, get as many SNPs as possible, as quickly as possible; and the other is to approve the technology for being able to detect SNPs, both to find them overall, and to be able to score them in large numbers of individuals. In order to allow this—in order to allow researchers to be able to find SNPs, we're putting together a resource. So, this is that box stuff in the top left-hand side there. We are talking about 450 U.S. residents. They're anonymous, in the sense that all information—there is going to be absolutely no information identifying these individuals; no medical information; no ethnicity information associated with these individuals when it is in the repositories (the repository is going to be Coriell). We want to have this be an ethnically diverse resource. It's going to be from U.S. residents. But by ethnically diverse we're talking about individuals with ancestors from various continents: from North and South America, from the Americas, from Africa, from Asia, and from Europe. And individuals whose ancestry is from mixed continents are fine.

And, of course, a lot of individuals in the U.S. have mixed ancestry. So, that's fine. As I said, no information is going to be associated with these samples. We're holding a very high, a very strict standard here about the anonymousness. The cell lines that we're using are coming in two sorts of ways. Cell lines that already exist. This is where we're cooperating with NHANES, that they have been very nice enough to share with us samples that they have. So, we're going to be getting European Americans, African Americans, and Mexican Americans, from the NHANES samples from around the U.S. There is also we're getting pre-existing collections of Native Americans. And for both the NHANES, and for the Native Americans, we're going back to those individuals and asking them for their consent to be part of this study. And you have the consent form in draft. It's not the final version yet, but it has been looked at by a lot of individuals. So, you have the draft consent form in front of you for that, which has the three pages of the consent form. And also, there are about two-and-a-half pages of additional information explaining what genetic variation is. For the new samples, we're getting consent as those individuals are agreeing to give their samples. Now, the goals of this RFA, and of the resource in support of it, is really—the driving goal is to find the single nucleotide polymorphisms, and to place them into public domain. We're very concerned, and you have probably heard about this, that companies are getting very interested in this, and we're very interested in making these single nucleotide polymorphism available to all researchers. So, there is a real urgency issue here about wanting to get those SNPs out, and in the public domain, in public databases. So, the point of this resource, and of this RFA, is not to relate these variations, these single nucleotide polymorphisms, not to relate them to disease, or to ethnicity, or all of those sort of other interesting things that you will want to do, but really simply to find, to discover, these variants. So, that's the goal of this resource, and of this RFA. Eventually, of course, the point of doing these—getting this resource, and of having this RFA, is so that later studies will use these variants that are found. These variants will be found. Technology will hopefully have improve a lot to make it very easy for individuals, so in later studies we'll expect that people will look at patient group, say, for particular diseases, and use the SNPs that have been found in this resource, and with this—the RFA, and use them in order to find the genetic basis for all sorts of traits. But those are going to be additional studies. Are there any questions?

DR. SHAPIRO: Dr. Lo?

DR. LO: Can I ask you two questions? First — well, first of all, I'll just make a comment. I think in the schema we're talking about, you're not in the upper left-hand box, but you're in the next row on the left-hand side. Because the original NHANES does have identifying information—that's the materials of the repository. You're taking a sample of that and stripping identifiers.

DR. BROOKS: Right. We're taking the samples from NHANES. We're only taking—we're not including any — they have, of course, a large amount of phenotypic data. We're not taking any of that. They are sending the samples to Coriell, and codes to us with sex and ethnicity; and then we're going to make sure we have a balanced sample, tell Coriell which ones to use; and then everybody is going to destroy any sort of coding there. But that's NHANES. There are also samples that are not coming from NHANES, where we are not going to know anything about the individuals, except their ethnicity and sex, and now we're going to get rid of that information.

DR. LO: First question: Technically, as I understand it, you could do this study with at least the NHANES data, without going back and getting consent under current CFR regulations. I applaud your going back and getting further consent, but if you could share with us the reasoning why you decided to do that, that would be important. Secondly, when you say later studies will relate the SNPs to medical data, are you intending that these later studies will be done on different samples than this group of 450? And what happens if one of those 450 has a very, very interesting S.P., or collection of SNPs, where some researcher says, "Boy, if we really could identify that person and get more clinical information, and maybe talk them into giving us a family tree and additional samples, we would be ten jumps ahead of the game." You're basically saying, "No, we're not going to do that." Even though you may have some high-powered technology that would allow you to say, "We know the ancestry. We know — we are guessing it came from the NHANES study. We could sort of rummage around it and find it. You're saying, "No, we're not going to do that." And, again, I personally agree with that. But was there a lot of pressure from researchers saying, "You're giving up an awful lot here. Are you totally going to shut the door?" At least I've heard that there may be other situations, not in this State, in other States, where researchers at the onset may say, "Okay. We don't need to know the people and they find something really dramatic, unexpected, say, "Well, we didn't think we wanted to go back, but now we want to go back. This code you gave us, which was supposed to be unbreakable, you really can't break it, if you just really devote a lot of energy and resources to it. It's really important now to do that," for whatever scientific reason. So, if you could sort of help us understand a reasoning that led you to these sorts of policies, I think that would be helpful.

DR. BROOKS: Right. To take your questions in their order, the first one was —

DR. SHAPIRO: Why are you consenting?

DR. BROOKS: Why are we being so strict? Partly, this is — the Human Genome Project—you have all heard of that—and that's going for the sequencing. And that's having very strict similar safeguards about getting individuals who are going to be sequenced as part of these libraries, and having consent for those individuals—even though they are also anonymous. So, it's following that same sort of very strict standard — partly, because this is a very visible project, and we want to really be absolutely ethical, absolutely unassailable — you know, "gold standard" sort of things—without—we are aware, and we are trying not to make this become the standard. We're simply saying, we want to be very, very strict. Without saying that we expect that this should be the standard that everyone else should use for every other study.

DR. LO: My question is: Why did you decide that? Was it just being cautious? Do you think the fact that this is all going to be in the public domain means that you really do need to get specific consent from the individual, even though it's anonymized? I mean, again, I'm just trying to sort of think through, is it just that this is the first one out of the block, so you want to sort of create goodwill, or are there more other than prudential reasons for wanting to be especially cautious?

DR. BROOKS: Well, we simply want to be cautious. It is going to be very visible. I don't know if Mark wants to add more.

DR. GUYER: I think the answers are, yes, to all of the suggestions you made. In addition, we've been concerned about the question that came up earlier about the distinction between identified and identifiable; that in the long term, although it's not possible now, ultimately, there may—these samples, because they are encoded by the unique DNA of each individual, they ultimately potentially could be identifiable, so that in this very early stage of the process, as we're starting to enter this era, in which, ultimately, anonymity will not be possible, we wanted to go very cautiously and make sure that were doing everything—that participants who were—whose material was being used in this were doing it with consent.

DR. SHAPIRO: Your consent form contains a paragraph—I only had a chance to read it quickly. I wish I had read it carefully, but I read it quickly. But going to the paragraph which says, "Yes, you might be identified in the future, if you provide additional information somewhere else. These things may come around the back door and be matched." Is that the sense of when you mean potentially identifiable?

DR. GUYER: Yes, a correlation in the future.

DR. SHAPIRO: Okay. We have got a number of people who want to speak.

DR. BROOKS: Can I answer the second question?

DR. SHAPIRO: Yes, please, go ahead. I'm sorry.

DR. BROOKS: There is essentially a very common question. Everybody who hears about this resource is horrified that we're stripping off medical information, ethnicity information, all of this really great stuff that scientists and doctors would love to know about. We understand that. In order to do a resource, where you actually kept that sort of information, especially the ethnicity information, that would take two to three years to have the sort of meetings, the sort of consensus, have groups—because if you're identifying individuals as part of ethnic groups, you have to decide what ethnic groups are; talk about group consent; understand group stigmatization issues. That's a very complicated process. Why did we decide which group who wants to be involved, who doesn't want to be involved? That's a very complicated process. It would be very interesting. But, as I am saying, given the interest by pharmaceutical companies in finding SNPs, we're very concerned that these SNPs get out and be in the public domain, rather than spending a couple two or three years getting a wonderful resource, while the companies are rushing ahead and getting all sorts of SNPs tied up in private databases. So, speed is one issue there. But the thing is, by finding these SNPs, as a large group of them, then researchers will be able to take these SNPs and look at them in their groups of individuals. Because in terms of applying it to certain diseases in 450 individuals, you can't begin to touch on all sorts of diseases. So, this is a first-step resource. By finding these variants, you'll then be able to take these variants and look at some group of patients and find whatever variants associated with diseases of interest. You couldn't do that. You couldn't get the

medical information in such a small sample. It would have to be zillions and zillions of individuals.

DR. SHAPIRO: Zillions and zillions, all right. Tom—okay, Carol.

DR. GREIDER: Could I just put the chart back up that we were discussing as a—So, just to bring this back to what we were talking about. From what I understood, you're using material that is in the upper-left, nonidentified, and also materials that is the next one down, coded, but not traceable, because you're throwing away the code.

DR. BROOKS: Because what we're saying with the NHANES —

DR. GREIDER: The NHANES is the coded, not traceable. And some of it is the nonidentified. And so, you just answered one of the questions, as to what is different between coded, not traceable, and encrypted, feed-forward and why. The answer that you just gave about it would be much quicker to do this study if you throw that away just for issues of expediency to use that, coded, not traceable, as opposed to the encrypted, feed-forward, or some sort of encrypted method. And I think that this is sort of one of the areas of debate that we're having, and it's going to come down to issues of how the experiments are actually done, and a lot of discussion with people about the differences between those two areas. So, I appreciate you telling us exactly why it was that you chose to be in the different —

MR. HOLTZMAN: And also, it's important to make clear that the goals of the S.P. project—and the nature of the kind of resource you're trying to establish—that the phenotypic information is irrelevant. You're just looking to map pattern, define common variants. So, it would make no sense to go through trying to collect for the reasons that have been cited. You are not going to get any kind of correlation of interest, unless you get up to 10,000, or when you start, and until you have 100,000 SNPs that can give you the mapping density. So, don't take this as a paradigm — this is the exceptional study where a piece of meat is good enough. Right? And the same way in which when you're going to — if you're going to look for a DNA sequence with the genome, just give me some DNA from a few people.

DR. SHAPIRO: That could be a subtitle of our report. Alex?

PROFESSOR CAPRON: While we have that up here, it strikes me that what you were doing, because you were creating a resource, which is another word for a repository, reminds us that we may have to add another level, or recognize that it can't exist. There is one repository, which is NHANES, the CDC's repository. You're going to be moving from that, in which we have identified samples, to create a new repository; and then once it exists, individual researchers will then be asking for material, or these SNPs will be established. This is going to be a reference material, right?

DR. GUYER: No, it's a database that simply says at this position in the genome, that there is a common variance of one in a thousand of the G versus the T. All right. It's not—there will not be a repository of samples. It's just like mapping information.

PROFESSOR CAPRON: Now, how large is NHANES? How many samples?

DR. GUYER: They have 8,000 cell lines. The actual sample is about twice that.

PROFESSOR CAPRON: And are you going to go to all 8,000 of those people? Using some random method?

DR. GUYER: It's complicated. There are two subsets within the NHANES. The first one is relatively small. And, actually, even for their purposes, not usable for anything else. So, we're going to go to all of those people, and then we have — in order to get the numbers up, we have to go to a few more from the larger set, which they are doing analysis on to identify some people in that larger subset, which, if removed, won't disturb their ability to use the larger sample for the purposes they want, so that taking the small number of samples out of the NHANES collection won't affect the ability to use the larger set for the purposes that the NHANES study wants to use them for. The cell lines that are removed, that are used, transferred into this repository, will not be used for any further studies, NHANES studies. They are going to be removed from qualification for the NHANES. So there won't be any additional data gathering on those.

PROFESSOR CAPRON: And out of your 450, how many do you expect to come from NHANES, as opposed to the Native American, or the Asian American?

DR. BROOKS: 310. So, the NHANES people will be approaching about 600 of their individuals asking for consent, expecting roughly 60, to 70, to 80 percent consent; and then, of those, we're expecting to get 450, which is a

different 450 than the total in this sample. So, for 450 individuals from NHANES, we'll get their consent from; of those, we're only actually going to use about 310.

DR. MIIKE: Why are you removing them? What is the point of removing them?

DR. BROOKS: The point is so that individuals who give their consent are not going to know whether they are actually in the sample or not.

DR. MIIKE: No, no, but you said you're going to remove them from the NHANES sample. What's the point of this?

DR. GUYER: Again, for the same purpose, that if — that, ultimately, in the NHANES study, they're going to want to do genetic analysis. And there will be a database for our resource saying, "individual sample 363 has a certain genotype," because those data are going to accumulate. If those samples were used in the NHANES study, that correlation could be made, and the link made.

PROFESSOR CAPRON: Now, what I think we should take from this, besides the detailed information you have provided, is a reminder in your decision to go through this process, that with a great many of the kinds of research issues that we have been presented—and I hope that we will get a chance to talk about these when we look, for example, at the Buchanan paper. We are talking about not a tradeoff between science and ethics, we're talking about what efforts and what resources we're willing to expend to achieve certain kinds of protections. Protections is even the wrong word — certain kinds of respect for the fact that a person is being — or their material is being used for a particular project. I take it that sort of the subtext of what you're saying is you have a sense that the Human Genome Project is still a little bit of a hot-button issue, and that the notion that I went in for a National Health and Nutrition Examination Survey, and then that I ended up being used to develop the Human Genome Project might surprise; and then 10, 20, 30 percent of people you expect to say, no, bother those people, to the extent, that they wouldn't want to be there. And so, you're going to the trouble, even though it's a lot of trouble to go back to these people, and some of them will have moved I'm sure, and some of them will be hard to find, and so forth, you're saying you're willing to expend that extra effort. And I hope we can keep that in mind as we talk about this; that we're talking about whole different sets of tradeoffs. It's not between doing something or not doing it. It's the effort that goes into doing it.

DR. EMANUEL: I think they're following these people anyway, so this is much easier. They already have them, that following them is part of the NHANES.

PROFESSOR CAPRON: Okay. I mean that—what you're saying is that money is already being expended to stay in touch with them, so it's easier to contact them. With any particular project, it is going to be, in other words, a balancing of how much effort. And you're saying that the effort involved here is less than it would be if you had a bunch of five-year-old tissue, in which you hadn't been contacted. I understand that. I'm not trying to say that because this is being referred to as a gold standard, that we would then say that it's applicable in all of the cases. But we're balancing the kinds of interest that Buchanan talks about in his paper against—well, among them, scientific interest, and the personal interest. That balancing isn't struck in a yes/no way, or it's impossible to do it. Well, it's possible, but it's more effort. Here you're saying it's relatively not that great an effort. I still applaud them for doing it.

DR. SHAPIRO: Thank you. I have Trish and Carol, and then I also — excuse me. I'm sorry. Diane Wagner from the CDC is here. She may wish to say something, but is not required to. Let me turn to Trish and—you're okay? Carol.

DR. GREIDER: In this discussion that we've had, it brings up to me an issue that it really depends on the background assumption about the protections in those different boxes that one assumes are there. So, if I interpret it correctly, the reason that you've chose to put — to go for the nonidentified and the code, but not traceable, was because the assumption was there would be a lot more background protection; that is, there would be more protection for those individuals, than if they had been encrypted, traceable and encrypted walk-back and feed-forward. If we had a mechanism whereby one felt that there were very good protections for people that were in those lower-down boxes, one might be able to then have better protections for the individuals, as well as more information for the researcher. For instance, I notice in the consent form one of the questions is, "Can I withdraw from the study?" And the answer is, no, you cannot withdraw from the study, because we're stripping—we don't know who you are. But if we felt that there were very good protection in the encrypted feed-forward and walk-back, then one could withdraw from the study. You

could take that person out of the study if they didn't want to be in the study. And if there was a request for more information, so that it would be more robust within the research side, and more robust in terms of the protection for the individual. But the reason that you're not going that route is that we feel that the protections aren't strong enough in those categories.

PROFESSOR CAPRON: That's not what she said. She said it would be a complicated process to get there. She said that there are issues, for example, about defining what the impact on groups would be that requires you to first figure out what the group is. What does it mean to be an African American, or a Mexican American, or an Asian American, or whatever. And that's work that they don't want to spend time doing while commercial outfits lock up the genome.

DR. EMANUEL: But also, Alex, beyond that, that once they do, what process and safeguard—I mean, as I understand it, they didn't know what the proper thing to do was, because we had — I mean that we, NBAC, hadn't defined the rules, as it were. So, they made the rules up by the seat of their pants.

DR. BROOKS: And I should add that as part of the planning process, the LC Group at Genome Institute is making dealing with genetic variation one of their priority issues, so that we actually have your good minds lurking about how to deal with ethnicity in an ethically acceptable and useful way.

DR. GUYER: I think it's fair—the last point is very true, that we didn't quite know what to do. And if there were better ways to assure protection to the individual, we'd be more than happy. We hope that the kind of lengths that we have had to go through in this case are not going to be the kind of lengths that people will have to go through to do studies in the future.

PROFESSOR CAPRON: I had just one question—is there anything in your resource that will link SNPs with each other? That is to say, will there be any correlations run on —

DR. GUYER: There will be a database in which the genotype—the S.P. data—will be linked to the sample itself, so that we'll be able to say sample 153 has the following SNPs, and that will be cumulative. And that was one of the reasons for doing this as a central resource, so that all of the work done around the country and around the world on these samples could be cumulative.

PROFESSOR CAPRON: And can you imagine in the future someone coming back to the resource and saying, "I didn't see this particular issue addressed?" Could you look at your samples again and tell me whether this S.P. is associated with the following other sequence, which isn't a S.P. sequence? But this XYZ gene that we know, is that something?

DR. GUYER: That is possible.

PROFESSOR CAPRON: Well, to me, then, the answer I got from Steve is not quite accurate. This isn't just a database which has data in it. It will be something where questions can be asked of that database on a biological level.

DR. GUYER: To a limited extent.

DR. BROOKS: Right. But researchers wouldn't go back to the database or say, "Would you do this?" They will have access to these resources.

DR. GUYER: The public will have access to the cell lines themselves, and to DNA samples.

DR. BROOKS: As well as the database. So, if you want to correlate some sort of gene with other SNPs in that database, you can get the DNA and —

PROFESSOR CAPRON: This is then a second level repository. The first level is NHANES, and this S.P. database becomes a new repository with data, which at that point, is not identifiable to any person.

DR. GUYER: That's correct.

PROFESSOR CAPRON: And on which subsequent researchers can do biological research, or the molecular research with the cell line itself.

DR. GUYER: That's right. And I think the concern that was expressed initially is that the level or degree of

research that can be done is probably relatively limited.

PROFESSOR CAPRON: Yes, I understand that. But it would involve another researcher saying, "I'd like to get the cell line to look at it in my own way now." Thank you.

DR. EMANUEL: Why isn't that a research sample? I guess I'm — as a researcher, that sounds to me like a research sample, not a repository. Okay?

DR. GUYER: Once you get the sample for your research purposes, we were conceiving of —

DR. EMANUEL: Well, let me just give you — the support study, for example, has put all of its information up on the Web, and you can go noodle around and do correlations you want on their data.

PROFESSOR CAPRON: They're going to passing out the sample themselves.

DR. EMANUEL: For the support study, there aren't physical samples.

PROFESSOR CAPRON: That's right.

DR. EMANUEL: That's all I'm saying. It's not a matter of critiquing it. It's just a matter that we were thinking of repositories being the kind of things that pathologists have, or that the people who run the blood spots for PKU have a bunch of stored material, and a researcher says give me some material. Here they have NHANES, which has that material, and they're going to be creating a new subset of material that's been removed from NHANES, which they now hold. And it's different. It's now unidentifiable — and add it to non-NHANES sources. That's right. This is going to be a new repository. It was just a subtlety that we had.

MR. HOLTZMAN: But I think it was a subtlety, which we're putting a lot of pressure on, which I don't think is important here, because it's going to go — those cell lines will now sit in Coriell, along with 100,000 other cell lines, where you can call up Coriell and order those cell lines, if you want to do studies of interest. The reason they have a specific — jump in here—sample is that they want everyone in the world working on the same sample, in order to define the SNPs. Once you've got the SNPs defined, there is nothing particular interesting about those cell lines. You are going to then take the SNPs, the definition of the SNPs, and interrogate samples of Alzheimer's patients, and diabetes patients from other cell lines. Because of the relevant clinical information that would have made those interesting is gone. The only thing that is useful for is now going into identifying more SNPs. Is that fair, Mark?

DR. GUYER: Yes, it is.

MR. HOLTZMAN: But the relationship between SNPs here is just where they lie in the genome, and with the frequency that one is associated with another.

DR. SHAPIRO: Last comment before I ask Ms. Wagner if she would like to address this. Bernie?

DR. LO: I have another question about the consent form and the considerations that led you to include, or not include certain things on the consent form. From what I gather, using it as a sort of tool for commercialization would be a pertinent consideration, whether they choose to be in the study or not. And, yet, that's not in the consent form. I was wondering if you could sort of think through — help me understand a reasoning for not putting that in, because commercialization is one of the things that's alleged as an interest some people might have in either joining, or a reason for joining or not joining this type of study.

DR. BROOKS: That's something actually we're discussing with the CDC people and with the IRB—exactly how strong to say this—because the previous draft did say about commercialization then — I don't know whether it's the IRB, or CDC who said, well, it's okay simply to talk about financial benefits. And so, we're actually discussing now does financial benefit include commercial? Because we agree that it's actually important to make that point. So, that's under active discussion right now, that exact point.

DR. SHAPIRO: We thank you. Ms. Wagner — there's nothing left to say? You're not required to say anything, but I just wanted to invite you to.

MS. WAGNER: I am not familiar with the protocol, so I don't think I want to say anything representing CDC. But let me just make a distinction that's come out in the conversation, as you think about that one box called "coded, nontraceable." And, as Mark pointed out, that is one of the considerations, in terms of going back and giving informed

consent, if it was going to be put into another repository that you have mentioned, and if there was a conceivably a chance of making it identifiable. And it wouldn't be identified, but it could be identifiable. There would be other studies I would see from that box where you might do sera, and just test one item. Those would never be identifiable. So, when you consider that box, remember that there are two ways you can get information from this. And, potentially, there are two ways that information about the person might happen.

DR. SHAPIRO: Thank you. I propose—first of all. Let me thank our guest. Thank you very much for coming today, and taking your time. We very much appreciate it. It was very helpful to us. We'll take a break in just a moment or two. And when we reassemble, I think it might be helpful if we looked at some other cases a little while. Steven provided Kathi with some, and David has some cases. And let's look at that and see, just to give us some experience with particular cases, then we'll return to the more general issues. So, let's take a break. Let's try to reassemble at 10:30.

[BREAK]

FURTHER DISCUSSION OF HUMAN BIOLOGICAL MATERIALS REPORT -

Dr. Harold Shapiro, Dr. Thomas Murray and Commissioners

DR. SHAPIRO: We still may have some Commissioners trying to check out of their rooms or something. So, why don't we just wait one or two minutes more, because I'd like as many here as possible for our discussion. I'll proceed with our agenda. As I indicated before, I have asked a few Commissioners to think of some cases that might be useful. And I'm going to turn to them in a moment to describe briefly some cases that we may—we help ourselves understand the kind of evolving structure we're using to see where they fit in that kind of a model, whether exactly that one or not is not critical, that kind of a model; and even considering these particular cases, what protections might seem appropriate in those cases, without trying to reach any final conclusion. Once we have done that, we will turn our attention really to the discussion of protections, and then begin really a lot of more serious consideration of what protections, what the catalogue of protections are, which may be appropriate in some cases, and so on, and see where that discussion takes us. So, let's begin right now with the cases. And let me turn to David, first. I think you have one or two cases you had thought about. It probably might be useful for us to think about.

DR. COX: As in the briefing book at the last meeting, some papers; and so, the details of that—we didn't get a chance to talk about last meeting. And so, if you want to go back for the actual papers, it's in your previous briefing books. And the specific case I want to refer to is a case that basically deals with determining the frequency of the BRCA1 mutation in the Ashkenazi Jewish population, and how that was accomplished. I'll at least give a minimal of background on this. The illustrative point, why I'm bringing up this case, deals with the issues of community involvement and community consent. And the lesson to be learned from it is, even in the very short time, over the past couple of years, is that the views of community involvement and consent have changed. So what's the example? The example has to do with there was some preliminary work suggesting that in one particular community, the Ashkenazi Jewish community, that there was increased frequency of mutations in this one particular gene, the BRCA1 gene. So, how could one graphically and efficiently confirm that to see if it was in fact true? Well, this was a situation where one didn't need to know the identity of the individuals at all. It's one of those cases that Steve Holtzman talks about all of the time, where that you didn't really need to know the individual people. You just needed some material from them, and you needed only one other piece of information, whether they were Ashkenazi Jewish or not. You didn't need to know anything else. You didn't need to know, in fact, whether they had breast cancer; or whether they didn't have breast cancer; whether they had a family history of breast cancer or not. That could have been interesting information, but the question that was being addressed was simply what was the frequency DNA changes in this population, and was it different from other populations. So, in order to do that, and to do it efficiently—are there samples available already existing, that could be used for this purpose? And it turns out that there were such samples available. And they were samples that had been collected for another purpose. They had been collected for two reasons. In one case, it's collected in families that have a history of Tay-Sachs disease, a separate genetic disease, in which that was really used—people could say whether it was used for research, but it was really used for clinical information, in terms of deciding whether people were carriers or not of that separate mutation. And those samples, those DNA samples, were available. The individuals, when they had that material used for Tay-Sachs, had had informed consents done with them, for Tay-Sachs, but no one had ever mentioned anything about breast cancer. There was a separate group of samples from another genetic disease, that individuals were known to be Ashkenazi Jewish, in terms of where the material was

collected, and those were individuals that had family histories of cystic fibrosis. Again, that was being done in the context of that disease. There was informed consent for that disease. But at the time that the samples were available, no one had said anything about breast cancer. So, those samples—both of those types of samples—were not just from one place. Some of them were available from Israel, some were available from different places in the United States, and the samples were available, the DNA samples in the researcher's labs, where they were—had the identifiers stripped off of them. So, in this case, they were nontraceable, they had been identifiable, but as the samples existed in the researcher's laboratory, and, as far as I know, with the original repositories, or the original owners, is that no one could go back and figure out who was who. So, this fell into the category of "not traceable." So, under the present regulations, these were exempt from any human subjects considerations, or any special protocols. And so it's stated, if you read in these papers, is that these were samples that were used that were fully in compliance, because they were consistent with the previous regulations; that is, that they could not lead to identifying individuals. What wasn't stated in the papers at that time, because it hadn't really been brought up so much as an issue, is that neither the regs nor people made the point that there are in fact group identifiers associated with this, that all of these people were Ashkenazi Jewish. So, what happened then with these samples is they were used without going back to these people, and to get a major of the frequency of DNA changes in BRCA1 gene. And there was no way of identifying individuals, but I think I don't need to tell anybody, or remind anybody on the Commission how that came out. It was in newspapers all over the place, that basically Ashkenazi Jewish people have an increased frequency of DNA mutations in the BRCA1 gene. Now, what was the impact of that? Well, it's hard to say. But it's clear that there were group concerns that were involved with that. So, for me what's the take-home message from this? This is a situation of samples where there was a complete firewall, because you could not get back to the unique identifiers at all. But—and it completely was consistent with the present Federal regulations—but, on the other hand, I don't believe they took into view a sensitivity of going back and getting group consultation, with respect to doing this. Now, that's because I'm not saying it was done wrong at the time, but that times have changed. So, then what would be the suggestion of how one could get group consultation? Which rabbi do you talk to, or who should you talk to? And so I have a suggestion, in terms of this, which comes out of exactly this study, is that this wasn't one group. It wasn't just like a big pot of Ashkenazi Jews. It was different local groups, which were different. Some of them had a family history of cystic fibrosis; some of them had a family history of Tay-Sachs; some of them were in the United States; some of them were in Israel. But each of those different subsamples had different representatives and different people contributing. And I would be willing to bet that each group would have a different view, in terms of what the group risks were. And so, for each individual group, although you may not have been able to identify and go back to the individuals, per se, what the group was known; and that it was possible to go back to that group and ask, not to figure out what all Ashkenazi Jews think, but what each one of the contributors of those samples thought; and that this case will come to Alan Buchanan's paper. But I think he's right on the mark, which is that individual rights don't trump group rights; but, even more importantly, group rights don't trump individual rights. And so, what you can do is do the compromise of going into the subsets of the groups that are contributing the samples, and ask each subset what their feeling is. And would this have been onerous? I think in this case it wouldn't have been so onerous. I speak as a researcher, because these were four specific groups, which you could have gone in and got the answer directly. What would they have said? I can't tell you the answer, because nobody asked them. So, that's my case.

DR. SHAPIRO: Thank you. Alta and Tom.

PROFESSOR CHARO: You know, speaking as a member of this pot of Ashkenazi Jews, I got to tell you that no matter how it is that you slice me up, as an Ashkenazi Jew, or an Ashkenazi Jew with x number of generations in the United States, or particular medical background, or whatever, I'd be shocked if you could find a single person I found to be a good representative of me. This is a perennial problem.

DR. SHAPIRO: I would also be shocked.

PROFESSOR CHARO: I don't reject the notion that there is a phenomenon called collective interest. I just have seen, as a lawyer and a law professor, so many other settings where the collective interests are implicated, whether it's in affirmative action, or it's in litigation strategy, where one group—I saw a presentation once about gay rights, in which one group of people in the gay community decided to pursue a litigation strategy that others viewed as being detrimental to collective interests. I have seen many discussions about the ways in which collective interest could be vindicated through some kind of process that allows for collective decisionmaking. And in every case I've heard so far, the cure is worse than the disease. The efforts to find a procedure to vindicate collective rights winds up having so many

problems in the determination of who speaks as a representative, and the degree to which their choices can trump individual choices, that in the end one keeps returning over and over to the individualistic model, not because we think it most perfectly represents the interest at hand, but because its like Mark Twain's definition of democracy, as the worst system of all, except for all of the others. And I'm extremely nervous about moving toward anything that smacks of—even a community consultation model that sets up a presumption against an area of research, because of the expression of disfavor by some people, who have been fortunate enough to be designated the community representative. I am not unsympathetic to the issues about stigmatization. I am just extremely nervous about any solution that depends on a semi-official statement with any force and effect.

DR. COX: And in these cases, both sides—because it's not someone from one of these subgroups, that basically is speaking for all of the other people, but it's informing members of the subgroup. They know who they were. And any individual who doesn't want their samples to be used can say so; and anybody that does want their samples to be used. It's more informing and having people make the decision, and who makes the decision. I'm not saying that some community—appoint a community leader for each of these. But it's making known the choice to the individual.

DR. SHAPIRO: Are you saying, David, you would just think that it should have been reconsented?

DR. COX: Yes. Well, it's complicated to go and identify each individual. There are different ways to reconsent. So I think, yes, to be reconsented, but at least to the point of views that the community, whose samples that was coming from in each local area, and the people knew about it.

DR. SHAPIRO: Okay. Tom, Bette, Alex.

DR. MURRAY: This is probably an utterly, hopeless, wish on my part, but I'm going to—I wish that we could publicly announce my wish that we could impose a kind of discipline on the discussion of the cases. The discipline is essentially this. What I want to know in each of the cases is that—David has additional ones, Steve has ones — can we use this conceptual schema that is still up on the screen, to say, okay, we know where it fits, number one? And I think the answer to that is, yes, it fits in the coded, not traceable box. Question number two is, does it adequately describe the—can we identify the interests, which are raised in this particular case. I think we can identify the interests. Now, David, that's layered an additional kind of interest, which we haven't, so much talked about today. We have talked about it extensively in the past, and, that is, that group identity seems to be relevant here in some way, even if we can't identify the individual. And so, number one is, do we know what—where it fits in the schema? Number two, can we identify the interests at issue here? And, number three, what protections strike us as appropriate? Those are the three things I'd like to get out of each of the case presentations. I think we've got one; two, I think we didn't exhaustively list the interests; and, three, we looked at one kind of protection. And we've had Alta expressing some reservations about you know at least one way of one sort of protection that has been proposed.

DR. SHAPIRO: Thank you. Bette.

MS. KRAMER: David, two questions. If you had gone ahead to get community consultation, number one, what would you have done by way of getting it? And how could you engage in reconsent? Because if I heard you correctly, you said that the samples were untraceable. That's number one. And the second question is: In the last analysis, the research has been done, the discoveries have been made. Do you, do we, does the public think that the Ashkenazi Jewish community is worse off, or better off having gained that knowledge?

DR. COX: I'll deal with the second one first. I don't know the answer to that. I don't know. Some people will tell you that they are better off, and some people will tell you, "Hey, the community is worse off." So, there is no consensus on that point.

MS. KRAMER: Just a follow up question to that. Does not now every individual Ashkenazi Jewish woman have the opportunity to choose for herself whether she wants to pursue this further, and, that is, be tested, or not be tested, and gain the individual knowledge?

DR. COX: Well, actually, the answer is she doesn't, and not because someone is preventing her from doing it, but there is a whole variety of access and economic issues.

DR. COX: And that's actually what the potential harms are. That's what people would argue about from one side, that people would argue from the other side. So, I think there is no consensus on that. Whether it's been good or

bad is the point. The question, which is, how do you go back to do the reconsent, is that these were individual groups that were known. Because, as is described in the research paper, the groups are very clearly identified. Not by individual name, but in terms of where these samples came from, the clinic where they would have come from. It doesn't state that it's the exact clinic, but it says the location. So, these are identified groups. And so, what would the reconsent be? And this is just my own personal view. I don't think it's possible to go out, and send a researcher out, and do a detailed form of consent to each of these people. But I do think what would be possible — let's say that I was the medical geneticist in the clinic that was doing the Tay-Sachs work. Then what I would do in that clinic, because I may not know anymore, exactly which of the samples. If I don't know exactly which of the samples were involved, then this is a problem. As I put it—that it's unlinked, so I don't know which one. So, then I could go back to all of the people who I thought were in the biggest group and say, "If you don't want your samples used, let me know." But in this case, you're quite right that it wouldn't work because I don't know who is who. So, as soon as these are unlinked, where no one knows anymore who it is, you can't give people the option of not having their samples be used. So, what you can do though, in this case, is go back to the broader group and get a feeling of what fraction of people would want their stuff used or not used. This will not be sufficient, though, for Alta, because the individual no longer has a choice anymore.

MS. KRAMER: Let's jump forward. Okay? The work has been done. Why are we worse off for that work having been done, and that knowledge having been gained? We are worse off because we don't know what to do with it, or the options of what to do with it at this point don't offer really good choices. But the problem doesn't lie with the work having been done; the problem doesn't really lie with the group about whom the information has been discovered any more than it's going to be with any other of these genetic investigations.

DR. COX: And I completely concur with you. This falls—the kind of reconsenting we're talking about here is basically the—I can't remember the exact words that Buchanan uses in his paper, but it's basically one of respect. So, it's not of being informed, but of being respectful for people to have their choice heard about whether the samples are used or not used. If you don't know, though, whose samples they were, then individuals can't have a choice. So, I've raised this as a case study, without sort of saying—I have just raised it as a case study.

PROFESSOR CAPRON: I think David's case study is interesting, but I think two issues have been—at least two issues are being confounded here. One of them is the question, which you were getting at, Bette, at the end, which is the implications of a finding. And those implications can be adverse for members of the group who are identified at the present moment. I would say that, in terms of the design beyond the consent issue—I don't want to rest everything on consent. One can imagine situations in which you would have to say it is wrong for a researcher to go about a process, given the situation, that if, right now, insurance companies were to announce that an XY degree of risk, we are not going to write insurance for people, life insurance, unless they will undergo certain tests. And if found through the test to have the gene in question, they are not going to get life insurance. We say, "Was that true of breast cancer?" They say, "No, the rate is too low and the population is not worthwhile our screening every woman who applies." If I told you it was five times as high in a particular group, yes, it would be worthwhile. So, if you develop the information, and say that's true of this group, however defined, then you input them at that risk. And I think that question has to be asked by the research community is that, given that circumstance, not the making of the investigator, that's an existing social circumstance, it's a question that would have to be asked. But that would be true if we were not talking about stored data, if we were going out and getting the research information now; that is to say, if the researcher was not in a situation where the IRB would say, you may not do this research, because you were imposing upon a group of people who are not able to consent—that is to say, all of the women identified as Ashkenazi Jews, and who were going to have this high rate, an unacceptable risk. And they said, no, this is—we don't have social circumstances that make this prohibited. It's a matter of choice. Then what would seem important to me would be when you approach an individual, asking them either whether their stored sample, or a newly collected sample may be used — you say, "Our objective in this research is to make an epidemiological sort of statement. That is to say, the prevalence of this gene, is it higher or lower in people of a certain descent? Is it, for some reason, found at a greater rate here? And that is a question which we haven't fully figured out—which is, how do we expect people to take into account the interest of others who are affected by their decision? That also arises in family situations. If I get screened, it has implications for my relatives, etc., etc. We recognize that as an issue, and that's one group where we tend to say the consent will handle it. I'm with Tom, however, in wanting to look at our chart here and to realize that what is—the Chairman has occasionally spoken as though we get down to a bottom line here. But I think we actually—what the chart will eventually show us is all sorts of questions that

get asked along the way; and then to loop back through questions. For example, here the question would—and so, you are under the nonidentified, or something, because we don't know any particular sample. But the question is, will the research results have implications for an identifiable group? Yes/no. And, perhaps, if yes, then we were saying then somehow consult with that group, or at least find out what the sensitivities of that group are, etc., etc. Now, or we may say, "No, you can't do that," because for most groups there are no legitimate representatives, and we just leave it to each individual. But those are the kinds of choice points on which we should be focusing, and try to move our discussion forward, beyond these sort of rough boxes, to the questions that get asked with yes and no answers.

DR. COX: That's exactly why I put this case study forward, because of the discussion that's come out, this is about as straightforward a one as you could in the box of not coded — or coded, not traceable. And where there are groups having said coded, not traceable, there are limited definable number of substantive people that those samples came from.

PROFESSOR CAPRON: Yes, I understand that. But it seems to me that there is a small confusion here in talking about the people from whom they came. If we were saying that you were now going to make statements about the congregants of Temple Beth El, then it would make sense that you would go to that temple and say, "We have sample which we collected when we did the Tay-Sachs screening 20 years ago. Yes, we would like to use them now for this other purpose." When we're done, people are going to be able, either because we're going to say it's Temple Beth El, or because the people will be able to know we were in Baltimore, and we were asking this group, and we know they know that Hopkins has those samples. Somebody will figure it out from the *Baltimore Sun* or something, and publish it that way. Then you are actually saying, "This group should be able to protect itself." But if you're using those samples, but you're not going to make any statement about that to a particular group of congregants at that temple; but, instead, you are going to be making statements about an ethnic population spread around the world, of whom this is just what you believe to be a representative subset, then you're in a different ballpark, it seems to me. Because then, while it makes sense to ask these people are they willing to have their samples used for this research, if they answer, yes, their yes has an influence on people who are not being asked. And you're, in effect, saying—and I'm not saying this is wrong. I'm just trying to spin out what to seems to be the implication. You're in effect saying that if you make it explicit to them, you expect them to weigh the harm that could be done to others, with whom they share a characteristic by these findings, or the good that could be done for those others, are we better off alerting this particular subpopulation that they should be tested more frequently for breast cancer than the average woman, because they are at higher risk; or are we telling them they had better buy their insurance today, because they won't be able to buy it tomorrow? I mean what are we telling them? Those are the kinds of considerations that we have. So, we have two different meanings of going back to the group. One is where you're going to make statements about this very group, and you have to ask them before you do it. And the other is, well, you're asking them as surrogates for a larger population, and your statement is going to apply to that larger population. And are they an adequate representative, or do we just say there is no way of getting that, and that's one of the problems that we have here? Alta quoted Winston Churchill, to whom she gave the name, Mark Twain, about democracy—yeah, Winston Churchill, I think. But, in any case, I want to quote Bernard Dickens yesterday, though, in saying that—reminding us that, even if there is not the very best way of doing something, there may be still a better—there may be — it may still be worth doing it. And, in this case, I'm not referring to the research, but the looking for the consent. I would still gather from this that it is better to have asked people who at least identify with the interest of the whole population, whether they think it's appropriate to go forward with the research, presupposing that it is. I mean to give a different example that Buchanan gives here. What if we were looking at the correlation between a group and violence, or "criminal behavior," or something. Now, the notion of that kind of thing, which has such racist overtones, could be done without asking people whose stored examples you have to have, as the next-best surrogates for the group interest, would strike me as wrong. Because if I knew my sample had been taken to make statements about Caucasian males' potential for violence—as opposed to Caucasian females' potential for violence—I would think that even though it's going to show that our potential is much lower, I would want to be able to know that I was in some sense contributing to that. And if I thought it was pernicious research to say, "You're going to have to find some other way of doing it. You're not going to do it with my sample, thank you very much. I think that still has, and still — I differ with Buchanan on this. I think there is a question where respect means the right to nonconsent, and that's — to me that's—I'd love to get—when we talk about his paper, because I do think there's a conclusion that he doesn't seem to reach from this, where it's worthwhile going to the person and asking, "Can we use your sample?" Because it would be research that I wouldn't want to have done. I wouldn't want to contribute to, even in an indirect way.

DR. SHAPIRO: Why don't we hold off. A lot of people want to speak. If we go in order, we can accumulate your thoughts and responses. Bernie.

DR. LO: David, I think your study is very illuminating, because it suggests that the model up there needs another dimension. So, I agree with Alex. There is a question — there is an algorithm or flow chart begins, or is it not identified community of collective, you might want to say, implicated. If, yes, then there is a whole new set of questions we haven't really sorted through. But I wonder if, again, using the analogy of community consultation and HIV research, suggest different meanings for that, than I think people are talking about. I think a lot of us are working with the assumption that you assemble representatives, or somehow will have the authority to speak on behalf of this community, and either approve or disapprove of the research, so that it's sort of parallel to the individual consent. There is community consent or approval of the research. I think Alta's concerns about who do you get, and are they represented, in what sense are they legitimate decisionmakers, are all very important and are solvable problem. I would suggest that the true value of community consultation is not that you could walk away saying they approve, it's an okay study, full steam ahead. But that if you don't ask, then you'll never — first of all, otherwise, the issues will get submerged. If you don't ask, you'll never find out what the concerns and problems are. And what we have gotten away from in the AIDS world is not—we want to do it; no, you can't; yes, we will; no, you can't. It's, look, we have a problem here. We'd like to solve it. There may be some concerns. If we understand your concerns, we may be able to design a better project. And what typically happens is not that the community representatives say you can't do it, they say, "Well, why are you doing it this way? We're concerned that this may cause that." And what happens is that you end up designing a very different project than you started with. So the consultation is not for approval, but it's to sort of strengthen the protocol. I would say it's not just to address ethical concerns and community interest, but also it makes a tighter study. It always is an implicit veto, that if we really don't like it, we will cause enough stink that you will be — you, Mr. and Ms. Researcher, will be so unhappy that you will withdraw on your own. I mean that's, in a sense, a threat, and it was used early on. But now I think it's less of a confrontation. The second way in which community consultation is really helpful, is not redesigning the protocol, but correcting the researcher's idea. David alluded to this. We've got a research study. Here is a quick, simple, inexpensive way of doing it. We've got all these stored samples. We don't have to go the trouble of collecting the samples. They are all there. It's just going to be a nice, efficient way to do it. And one of the things you learn doing this kind of research is when the community is involved, there is no quick and easy solution. So, what the community typically says is that we have no problems with this being an important question. We have no problems with your integrity as a person to do this research. We have a lot of problems with what this means, what the misunderstandings might be, what the implications might be. The issue isn't are we better off doing this research, or not doing it. The real issue is, can we do this in a way that addresses some concerns and questions we have. And, typically, what evolves out of these meetings is the sense that it may be cheaper, in terms of, if you don't have more efficient, you don't have to collect more samples. But the researchers end up doing a lot of things with the community. So, they go to community meetings, which may be open community meetings, where they just explain what BRCA1 is, what it means. Does it mean I'm going to die of cancer? Should I be tested? They probably are going to be asked to have more specific meetings with the rabbis, or people who are in community-based organizations that serve that community. Because it can be expected that when the results are known, people similar to the people of whom the studies — will have questions about what it means. And that's clearly not information that the community knows, but it's information the researchers know. And the researchers get educated, in that they have an obligation, not just in the research and get out of the community, but to make sure that the people who have—will be directly affected by the implications of the research understand what it means, and have their questions and concerns addressed. So, you end up saying, "No, you don't have to collect the samples," but you spend a lot of time going to community meetings. And it's part of the price of doing research on a population that's particularly suited for the type of work you're doing. And just educating researchers that that is part of their role—it's an obligation that's important—and that really only comes from these community consultations. There is also—another thing that happens is the researchers begin to broaden their role to include, not just doing the research, but how they write it up, how they talk to the press about it, and how they get involved with policy implications. So, again, going back to the AIDS example, early on the community said, "In addition to our concerns about how you design new studies, and your lack of providing education and information to the community, we're concerned that you guys aren't speaking out on the real policy issues, which have to do with discrimination, confidentiality, funding for AIDS research, all of those other issues that are — you know, in the minds of some community leaders, linked to the outcomes of the research. But researchers typically say, "That's not our job. That's policy. We're just scientists in pursuit of the truth." So, I think to me the true value of the community

consultation isn't that you collect a bunch of people who vote, yes, and it's okay. But that from having asked the questions, and had people talking to you, you have hopefully changed what the researchers regard as their role, and their obligation. And it's particularly important in a situation where you are going to be going back to these people just because of these genetic quirks, and this population that made them so efficient a group to study for these diseases. And it's like the international researchers we talked about yesterday. You don't just do the study, take advantage of the community and get out, you have an ongoing relationship, and researchers need to learn that. And, frankly, having real live people in the community, these are not representative, and they may not represent precisely anybody but themselves. The fact that they are talking to the researcher face-to-face means the researchers are more likely to listen. So, I think we need to — you know we sort of not define what we mean by community consultation. I think it's not really analogous to community approval or consent, the way it is for individual consent.

DR. SHAPIRO: Okay. If understand what you're speaking about, Bernie, which I—in which you've been quite eloquent. It really is—what you have described takes place in a process of study design and formulation of the study, and it has impacts on everybody in that process, I understand. Carol?

DR. GREIDER: Bernie made the point that I was going to make and he made it very eloquently, so I won't go much further, except to say that we did have in the Genetics Subcommittee when we met, Dr. Killen, I believe. He was from the NIAID, who spoke very eloquently about this. And, in fact, completely changed my mind about the issue of community consultation. I was struggling with the kind of things that Alta was raising about how do you get people to actually consent for something, for a group, and that sort of stuff. And when he presented what Bernie just summarized to the Genetics Subcommittee, I was really impressed with the idea of involving a community in the research, in the way that Bernie just said. And so, perhaps, my fellow Commissioners could go back and look at the transcript from that meeting, and look and see exactly the details, and also for the report about community consultation. I think he was very eloquent on this topic, and maybe we can just review that.

DR. SHAPIRO: Okay. Kathi, do you have something you want to say?

DR. HANNA: I just wanted—some of the clarification I was going to ask for has already been made. I just wanted to raise two points. One is that the Commission think about consistency between what they're going to say about community consultation in this document, and what they anticipate they might say in the international document, and there not — that there not be two sets of standards, one respecting a democracy, and the other not being as sensitive. But the other thing was I wanted to just ask how—since we're on the issue of community, how we should proceed in preparing something for the next report, whether it would be useful for staff to go ahead and start drafting what we know from the literature, what's been reflected in the discussions, and proceed from that point of view. Would that be the most useful approach?

DR. SHAPIRO: I think it would be useful. I don't want to get us off to just discuss that particular issue now, since there are other cases we'll want to get to. But I just want to indicate that, in my sense, I think I support everything Bernie said, or, at least some of it, but I want to support everything he said. It really is—there is something in my mind which is qualitatively different from that, then what we have normally been calling protections, even though I understand that it may be even more important than the protections. So, it's no question, one being more or less important, but it's just qualitatively different. And as we think about it, we have to think of the right conceptual apparatus, as to where to put it, and how it should be reflected. Because I think what I sense around the table is everyone is concerned with the issues Alta raised, and we don't see any resolution to those issues that Alta and others have said. But this is really a qualitatively different dimension of the issue. And so, we'd have to think of the right conceptual framework just to incorporate it. Tom?

DR. MURRAY: Some of the elements, obviously, of the comments Bernie has made, the kinds of things that Jack Killen shared with us... the pieces of Alan Buchanan's paper, which are making I think a very good effort to tease apart the notion of the interest of a particular group of community, and begin to understand that there is really several interests which are distinct — related, but distinct. There is also a concern, a paper I will share with you, recently given at NIH by a colleague of mine, Eric Juengst, which I think expresses some concerns, which we—not today, but we'll need to think about before we bless the notion of community consultation—about concern that we not symbolically or otherwise contribute to a kind of genetic reductionism by assuming that genetically defined populations' themes are the same as culturally defined populations. Put those pieces together, and I think a draft at this point would be quite helpful. Alta?

PROFESSOR CHARO: First, are you sure Winston Churchill wasn't quoting Mark Twain? It is so unnerving when you were sure you knew something.

PROFESSOR CAPRON: I only know it because Zeke agreed with me.

DR. EMANUEL: It's just confirmatory data.

DR. SHAPIRO: What do these men know anyway?

PROFESSOR CHARO: I'd like to ask whether people have in mind that community consultation is something that is a backup with individual consent and dissent was impossible, or whether it's supposed to be present, even when individual decisionmaking is possible. The reason I asked that we reflect on this is because there is going to be a great deal of opportunity for individualized consent and dissent, I believe, when we begin to break this out a little bit. First, for all sampling of human material from here on out, even before this Committee and many others come up with recommendations, I think any sensible sampler would take advantage of the most broadly drafted consent form possible, and I have seen examples of ones that are very good on this, in which they ask people if they're willing to have their sample viewed indefinitely into the future for a variety of as yet unknown research protocols, including some that might implicate group stereotypes, and it gives people an opportunity to say, yes or no; and then the repository to have that consent form and that particular human biological materials is ever after able to know whether or not that material should be released for particular protocols, which means that we're really dealing only with existing collections, and those people who are silly enough not to start doing this right now. For existing collections, there are good reasons why existing collection repositories are doing that now because it's a way to avoid an awful lot of the messy problems that are going on and they can have a reconsent for a variety of future things that allow people to say yes or no to indefinite, future, wide-scale things. Which leaves only the residual of those people who have been unfound, whose materials are in existing collections as the ones for whom we don't know what their individual attitudes are. And there the question becomes, should you have a presumptive consent or presumptive dissent for any particular kind of use, and that's the setting in which, if community consultation is a backup for lack of individualized decisionmaking, that's the place you'd be using it. I don't know what the actual number of those people is going to be, but it's certainly smaller than the complete universe. On the other hand, you might all be thinking you want community consultation in conjunction with individualized decisionmaking, and that's a whole different story. It would help me to understand how tolerant I am of the problems associated with community consultation if I knew the scale on which we were going to use it, and the degree to which we're going to let it substitute for making a genuine effort to get individualized decisionmaking.

DR. SHAPIRO: David wants to say something in a moment. I just want to make a comment, at least on how I'm thinking about it. I simply don't look at it as a substitute for consent, except in very unusual and particular circumstances where it might be appropriate—I haven't thought that through. But I'm not thinking about it at all as a substitute for individual consent or as, well, just say that. The question is, in my mind, can the kind of interactions that Bernie described improve the overall quality of what's going on and answer the needs and maximize the benefits, minimize the harms that attribute to any particular groups by behaving the way Bernie indicates. That's my own view. But now, it's not clear to me if that's the case, if that's the model we're thinking about, it's not clear to me just what focus it should have in the report. That's why I mentioned it - I'm not quite sure what the conceptual framework is, because a large part of it goes throughout the process, as Bernie said. Both planning it, carrying it through, follow up. It has impacts every where, it impacts on researchers' ideas and so on and so forth. That's of a different dimension—that's the only word I can think of right now—than the kind of thing that's consent that we normally talk about. So it's a different, it really is a -

PROFESSOR CAPRON: It really is a consultation.

PROFESSOR CHARO: Perhaps I just did not make the question clear. Let me try very briefly to clarify what I'm asking. There are going to be many opportunities in the future and still today to go back to individuals and simply say, "What do you want? Do you want to allow your stuff, even if used in an anonymous, unlinkable-back-to-you fashion, do you want to allow it to be used for things that you may find pernicious?" Yes or no. And I'm asking if we could do that for most people. What role does this community consultation still play after these people have been asked what they want. I understand the debate about community consultation where you can't ask people. You can't find them to ask them. But I'm not sure I understand the role of community consultation where you can ask them.

DR. EMANUEL: Maybe I can—I hate to jump in here, but I will. Sorry, Eric. As I believe the Subcommittee

was discussing it a long time ago, it was in addition to any potential individual consent in the context where research might not implicate anything about an individual but might have implications for a community. So even though you couldn't identify the individual, as David has made quite clear, you could identify a community where your research result will have implications and could adversely or positively affect their interest. And the idea of community of consultation, which has evolved, was an effort to understand and also to revise, reform, refine the research and maybe not even to do it. Depending upon whether it affects, and how the community views the effect. It is not a substitute for individual consent, but it mainly arises in the context of research, which may not be individually identifiable, but as community, it is targeted at particular communities that are definable.

PROFESSOR CHARO: It's not about linkable to people—I understand that. But you could ask me whether I want my stuff to be used in the future, even when it can't be linked back to me. I can already have told you what I want, whether I want to be implicated in this research or not. I'm asking why then do these arbitrarily selected representatives get to decide?

DR. EMANUEL: Here's the issue, because you are convinced that any time that you can decide and your rights are implicated, that whatever the group is, if you give the group rights, that's just going to be an unworkable solution. I don't think that everyone necessarily shares that view. And what you decide as an Ashkenazi Jew could have implications for me or other people and they could be quite adverse for me. I think the question was, beyond the individual, there are significant group concerns. I guess, at least as I heard it from the Subcommittee, there wasn't a shared view that, "Well, we understand it might have implications for the group, but we're going to rest everything on individual consent." There was a sense that the community needs to be involved in participating in the design and decisions as well because the community is going to be implicated as well.

DR. SHAPIRO: Let me make a suggestion here since this is an issue which we're going to have to resolve and think about carefully and articulate. And I think the next best place to articulate is in writing and see how it looks and let's see how we feel about it. It is a very difficult issue; it's not an easy issue. But let's try to articulate that in writing. There is quite a fair amount of literature in this area by now and let's see how we can attach it and see if it makes sense to us. And I don't mean to so arbitrarily cut off, but we just have to get on. But we're going to be returning to it—it's not resolved, we're not resolving it. But I want to just give David one last shot since it was his case he presented.

DR. COX: And I'll make this very brief. It was a case study and I presented one side. Now, I'd like to make it very clear what I actually believe in the case of community consultation. The discussion was extremely interesting to me and Bernie's comments, which resonated with everyone, didn't have anything to do with the case that I presented because they dealt with something that could be dealt with prospectively. If you've already used retrospective samples where you can't identify the people, they can't be involved in the research design. So I really support the idea of community in the context Bernie was talking about. I use this example to try and, in the best way that I could, talk about how you would have community involvement with retrospective samples where you didn't know who the people were. And for precisely the reason that Alex says, I have difficulty with this because it confounds who the individuals are versus who is speaking for the whole group. So for me out of this discussion, it reinforces my own belief that community consultation in the case of coded, nontraceable samples where you don't know who the individuals are, I don't know how the hell you do it. But I do understand how you do it in other boxes. So that's why I use this example because I wanted to try to have some better insight and I didn't find it.

PUBLIC TESTIMONY

DR. SHAPIRO: I think there is a way to do it if one favors it, but let's wait until we've got it written down so we don't discuss it any further right now. Okay. Now we have scheduled in just three or four minutes from now public testimony. We have four people who wanted to speak to us. I'm going to suggest that if they are here now, that we begin right away because we really can't take on other cases in that short period of time and I don't want to keep them longer than our scheduled time. So let me just see, is Ms. Judith Brundin here? I just want to remind everyone, step forward to the microphone here if you'd like to. Just to remind everyone of the rules under which we operate in this area. That is, everyone has five minutes to present their material. If they have any additional written material that they'd like us to consider, they're more than welcome to submit it. And there is, of course, you did submit something in advance in writing, and every Commissioner has copies of what you submitted.

MS. BRUNDIN: You've given my name: Judith Ann Brundin. I'm from Union City, New Jersey. I am grateful

today for the opportunity to give testimony before this Commission because I believe its research objectives to be of extraordinary importance and the passage of John Glenn's legislation, a significant step toward unraveling human rights abuses within our own borders. My father worked as a space systems division senior administrator with Astronaut Glenn in the late '50s in Los Angeles. I grew up in what was known as the Air Force's "elite class" amongst a highly educated military group of Ph.D.s and Master's degrees. But by my mother's recent admission on audiotape and my own recollection, I was a victim of the Monarch mind control programs of the Air Force. And this occurred, in part, while my father was working with Senator Glenn. Because of this brutal mind control torture, I have become toughened, resilient and determined to bring out what has happened to me regarding this brutal assault and the continuing ongoing situations that I have suffered, especially since 1993. I am well educated; I have two Master's degrees. I am an author. I got past the Monarch brain control programs and I have done well until recently. In brief, in 1993, three men, who I know, with the involvement of government agencies, carried out mind control assaults upon me at work, in my Federal facility at the Smithsonian Institution in New York City. This included the implanting of an experimental device in my body, which is seen on X-rays. And, the man responsible for that in part was a Canadian paramilitary man named Robert McDonald. He has admitted to involvement with government agencies and was paid to set this up. This is the beginning of a brutal, high-tech community war which I have endured, which has included the use of chemical weapons and frequency weapons. I have suffered permanent physical illnesses in very short and quick time. The complete loss of four fetuses for unknown reasons. The chemical assaults have included toxic food poisonings consistently in my residence. I own a beautiful Victorian house. Arsenic was found in my foods on my desk at the Federal job, and that was by lab reports that me and my attorney did. Triphenylphosphine, a highly toxic chemical, was found on my steering wheels to my cars consistently—has been now for four years still found on the car. I wear gloves driving my vehicles. I have been used in Monarch-style mind control programs in those Federal facilities in 1993 and I was used further in sessions in Paris in 1996. The evidence I have includes toxic and exotic lab results of poisons found on Federal premises for which I had no access to. They were obtainable only by qualified chemists. Audio reports I have, some supportive eyewitness testimony, photo documentation, some police reports. I am still subjected to criminal syndicate cell assaults in and around my residence and food poisonings. I filed five court complaints in an effort to obtain a thorough investigation. This includes an Office of Special Counsel whistle-blower complaint to Janet Reno's office in D.C., which is still pending and mentions McDonald in four affidavits. Law enforcement agencies repeatedly ignore my pleas for safety and assistance. In lieu of my attorney not appearing here today, I am going to provide the Committee with a package of materials that includes a summary of my court litigation and newspaper articles which I have published in *The Washington Post* and many other articles that I have written about what's occurred to me. The research I now know that there is a mind control victim profile. Often, victims experience long histories of abuse, including abuse by family members. Their residences are nearly always surrounded by neighborhood perpetrators. Victims suffer intentional sabotage in terms of economic situations. I have endured $150 in damages of vandalism to my house in three years. After the abuse that these victims have endured, their ethical sensibilities are often extraordinarily high. I found probably four or five dozen victims like myself of experimentation—government experimentation and medical community experimentation—to be the brightest and some of the most moral people you have ever met. Who is paying for this system of human torture and genocide? It appears to be your tax dollars, people. Who is carrying out these vicious games of slavery and violent assaults in communities, because they are going on in this country? It's probably your government and, I'm not sure, crime syndicates is the next possible answer. It would appear that the corruption and mental illnesses in these scenarios have very little to do with these victims and a great deal to do with an ineffectual politic. As a supplement to my testimony, I submit to you the following resource materials, including summaries of my situations, information about my court cases, and the evidence and documentation I have been able to put together. I have lost my job, my career. I am dealing with violence now and ongoing in my life. It's very real, people. I feel that the mind control horrors our society has so quietly accepted through legislative inaction includes the loss of a great deal of life. This has got to stop and these policies have got to change and these stories have to come out. They have to hit the front pages. Thank you.

DR. SHAPIRO: Thank you very much. We very much appreciate the time it took to come today and if there are any supplementary materials you have, we very much appreciate having them. Any questions from any members? Thank you very much. The next person to address us at this time is Mr. John Cavanaugh O'Keefe from the American Life League. Mr. O'Keefe?

MR. O'KEEFE: Thank you Mr. Chairman. For the record, my name is John Cavanaugh O'Keefe. I'm the Director of the American Bioethics Advisory Commission, a project of American Life League. I want to thank you very much for the decision on the fourth initiative, the fourth paper you are undertaking. I think that was a great decision. I

think the topic does matter greatly and I'm grateful to you for the decision to go ahead with it. I do have several concerns that I just wanted to raise about it. In testimony yesterday, there were a couple of concerns that would obviously be of interest to Pro-Lifers and folks on my side of the issue. The suggestion that the Commission should explore population control or throw its prestige behind population control efforts would be of great interest to us and I wouldn't suggest it. If I understood Professor Dickens, he was also urging you to push ahead implementing the decisions in Cairo and Beijing. I think that that, too, could be a red herring. I think it would be a mistake. I think it would be divisive and unnecessary. I was fascinated by the material, by the suggestion that you explore further a new paradigm for research and inclusion of subjects in research. Subjects have a right to be included or a right to be protected. It seems to me that it's a little premature, perhaps too suddenly optimistic to adopt an inclusive paradigm now. That just seems too optimistic to me and the fourth concern coming out of yesterday was that I think that a public health model rather than a medical model raises a whole series of issues about dealing with a collective rather than the rights of individuals. Questions that go back right through the entire history of the public health system in the United States. All of the issues there have to do with eugenics. Frequently, watching the work of the Commission, I have this feeling that I have this five minute message tied to a rock and I'm trying to toss it over a 40-foot wall. Perhaps the easiest thing to do is if I just back up and point to a paper that does lay out the concerns really clearly. It's a paper by Major General Frederick Osborne published in *The Eugenics Review* in 1956. I will make it available to you all, but do want to just note three things about it. In his paper, Major General Frederick Osborne, a member of the American Eugenics Society, talked about restructuring the eugenics movement after World War II. And Osborne is usually credited in histories of American eugenics, as the reformer of the movement, in particular, that he drove out the white supremacy that had tainted the movement for 50 years. But doing this so called "reform," Major General Osborne was the president of The Pioneer Fund, which was a secretive, white supremacist group. And if he's the reformer, then what you're going to be left with is that white supremacy could remain, but it'll be secretive rather than open. If he's the reformer, the reform is a sham. I think that it's worthwhile when looking at his paper, looking at two things in particular. One, his description of what he called crypto-eugenics and looking what he urged as a new policy of voluntary unconscious selection, pushing for the eugenics movement in the second half of the 20th century. And I think that his ideas show up, in particular, in two places that are worth looking at in American-funded research overseas, the concern of this new paper. I think his ideas show up, in particular throughout the Agency for International Development. His work, I think, shapes a great deal of it and, in particular, I think it's worthwhile looking at Norplant. I think that the testing of Norplant overseas in American-funded projects does provide a rich source of problems and questions that should be dealt with as we think about how to protect human subjects. I will provide more material in the mail as soon as I can. Thank you very much.

DR. SHAPIRO: Thank you very much, and thank you for being here today. We look forward to receiving those materials. The next person to address us is Dr. Adil Shamoo from Citizens for Responsible Care in Psychiatry Research.

DR. SHAMOO: Although we recognize that the draft of research involving persons with questionable decisionmaking capacity—

DR. SHAPIRO: Excuse me, if I could just interrupt you for a minute. I do want to thank you and remind Commissioners that there is a letter that Dr. Shamoo provided us with. You may want to consult that. Excuse me for interrupting.

DR. SHAMOO: Although we recognize that the draft of research involving persons with questionable decisionmaking capacity are working paper of NBAC, is but a work in progress, we must express our extreme disappointment in what is lacking in this working paper and offer some of our concerns and recommendations. One, a fundamental principle of public policy and government business and academia is independent oversight and accountability. The absence of such independent oversight in human subjects research is especially harmful for mentally disabled human subjects, who are incapable of protecting their rights or their welfare and who have no representation on any public policy boards, including NBAC. We urge the Commission to recommend establishment of an independent Federal human subject oversight authority, such as a laboratory animal has, not NIMH. Independent oversight is the only method of improving safeguards. Unless the Commission recommends the addition of independent oversight, including independent capacity assessment and independent physicians to provide ongoing medical monitoring and independent onsite inspection of the subjects of research, not just the paperwork, it will have failed to make any improvement to protect disabled human subjects. Nothing short of independent oversight will protect vulnerable human subjects. Two, if the Commission is reluctant to recommend the establishment of a Federal human subject oversight authority, our organization offers a plausible alternative: a no-fault personal injury insurance requirement. Every human subject of

research should be protected in the event of harm by a no-fault personal injury insurance in the amount of, let's say, $250,000, with premiums to be paid by research sponsors, investigators or their institutions. Three, the draft working paper is silent about documented evidence of ethical violations, which has been presented to the Commission by individual families and patients on September 18, 1997. It is silent about published evidence submitted by our organization documenting 1) the absence of full disclosure of risks on consent forms, 2) evidence that consent forms are presented to acutely psychotic patient subjects, 3) evidence of violation of protocol exclusion criteria, 4) evidence that experiments are designed to exacerbate these evident psychotic symptoms by abruptly withdrawing medication and/or chemically provoking relapse. Amphetamine, apomorphine, ketamine ("Special K"), L-dopa, methylphenidate, MCPP, PCP ("angel dust"), cocaine, and fenfluramine are not therapeutic medications. They are dangerous psychosis chemicals. Yet, the consent forms we have examined mislead disabled subjects by stating the opposite. In no field of medicine are severe symptoms of chronic disabling illnesses chemically exacerbated for the sake of scientific progress. Patients suffering from multiple sclerosis or muscular dystrophy are not subjected to symptoms provoking challenge studies that are likely to exacerbate their symptoms. Diabetic patients are not subjected to insulin withdrawal experiments followed by glucose analog injections to inhibit the delivery of sugar to vital organs for purposes of studying the path of the physiological course of the illness or to see who would relapse. Why are such symptoms exacerbation experiments permissible in psychiatric research? The Commission cannot ignore the evidence; it must address the obvious. Why are uncomprehending, disabled patients easily recruited into experiments which clearly conflict with their clinical best interests? Is their mental disability being exploited? 4) The working paper ignores evidence of the inordinate difficulty for the public to obtain information about human subject research, even from NIMH, the agency entrusted with the responsibility of evaluating and funding such research. We have submitted a copy of a list of published troubling, possibly unethical, nontherapeutic experiments for which we were seeking informed consent documents under FOIA from federally funded institutions and from NIMH. Our original request was September 30 and subsequently February 12. To date, NIMH has not forwarded a single informed consent document for its own experiments and those it has funded. What are they hiding? 5) If the Commission presents a premature report to the public, a report that does not reflect relevant information known and available to the Commission, it will not engender public confidence in the Commission's recommendations. We hereby submit in 1997, a published report of a federally funded experiment conducted at New York State Psychiatric Institute, fenfluramine was infused into 34 6- to 12-year-old—I repeat, 34 6- to 12-year-old inner-city, minority boys, of whom 44 percent were African Americans and 56 percent Hispanic. The dubious purpose of this experiment in which the subjects were innocent brothers of convicted felons—they have no illness, they have no disease—was to prove that, and I quote from their paper, "biological factors, abnormalities in the serotonergic nervous system" predispose them to aggressive behavior. This experiment, conducted by the Department of Child and Adolescent Psychiatry and Biological Study Unit of New York's premier psychiatric research center, is being examined by Lawyers for the Public Interest and civil liberties attorneys in New York. Thank you very much.

DR. SHAPIRO: Thank you very much for your comments. We'll certainly think about these carefully and we will, of course, be reviewing some of these issues this afternoon.

DR. CHILDRESS: I'd like to thank Dr. Shamoo and others who have presented very important information for us and we've worked on the report that has gone by various labels, including the draft you're looking at on persons with questions on decisionmaking capacity. What's been provided has been very important, including the information we received on September 18. Even though the draft report does not focus on specific cases and discuss them in detail, I think what was provided that day was really very important for the way the Commission understands the problems and also the way it's going about thinking about possible solutions. So sometimes, even when things are not reflected specifically, they play a very important role in the way the Commission goes about thinking about the problems and solutions.

DR. SCOTT-JONES: What I have to say is similar to what Jim just said, and that is that we feel a great deal of compassion—at least I do, personally—regarding the individual cases that we've heard. But my understanding of our task is that we are not to address or look into those specific individual cases. So I believe they have, in fact, affected our thinking. And regarding the study that you mentioned at the end of your testimony, that study involves children and we're not directly addressing regulations for children in this particular report. We have talked about doing that at some point in the future. And I want to say that I have, in fact, read the study that you mentioned and I am quite horrified by it myself. So your concerns are not being unheard.

PROFESSOR CHARO: Regarding your suggestion of a no-fault compensation fund, are you familiar with any

example of its use in another country, an American State, or even an institution that has chosen to go this compensation-fund route?

DR. SHAMOO: No, I don't.

DR. SHAPIRO: It's also an example of where the health system in which we are all operating makes a big difference.

DR. SHAMOO: But the independent oversight is available in the Animal Welfare Act and that exists in the Department of Health and Human Services.

DR. SHAPIRO: Just one final comment I'll make is that we are in the process, in fact, of reviewing a number of cases of direct concern that will make its way as we go along into the court. I'm not reflecting any individual case here, but we are looking at that literature right now. DR. SHAPIRO: Any other questions from members of the Committee? Thank you. The final person that I have on my list is Professor Karen Rothenberg, who is here to address the Commission.

PROFESSOR ROTHENBERG: Good morning. Thank you, David, for raising that case study and I would like, if I could, just to raise three or four conceptual challenges that maybe the Subcommittee has already addressed and maybe it's in Alan Buchanan's paper. So I apologize, but maybe I could reinforce them, perhaps. And these comments come from two years of experience of working with the breast cancer community, as well as the Jewish community. In part, it's a reaction to this study. But the same case study could actually be utilized as well, most recently at Johns Hopkins with the announcement of the colon cancer gene, which also, in part, the data was generated from Tay-Sachs samples. The first conceptual challenge that I wanted to clarify, I think, is based on some of Alta Charo's points, is that community consultation is helpful after you've started, but it really matters before you decide to do this stuff. So you want to get the community involved in the discussion, 1) it will make it a better study; it will make it better for recruitment. An example of that is actually what NIH did in its recent Ashkenazi Jewish study, where they got over 5,300 people in a period of 6 to 8 weeks—unprecedented. They brought the Jewish community in ahead. There are some concerns about whether or not that is the right community, which I think are legitimate questions, but it is an interesting model and you may have already heard about it. If not, I would really encourage you to bring in the people from the National Cancer Institute, perhaps even some of the people from the National Action Plan on Breast Cancer, who were involved as well with that, and to talk to them about how they developed that process. Part of that process included that in the individual consent form, it said at the end, "Can we keep your samples for future studies of cancer?" And I think really is important based on the other point about behavioral genetics and using genetic and DNA samples for other things. So that would mean the National Cancer Institute could not give those samples to somebody who might want to study homosexuality or manic depression or whatever without going back. And they don't have the names of these individuals, the names have been taken back. So that's an interesting possible process you might look more into. So first point is, community consultation matters the most before you approve the protocol. Yes, you can continue community consultation while you're doing this study. Yes, you can continue community consultation after you've gotten the results of the study. A critical point is how you present the data to the public once the study is done, and there has been a lot of criticism about the use of the media in this context as well. The second point is, I wanted to clarify some additional facts. The Tay-Sachs samples were gathered by individuals in part, not all. They didn't consider themselves a research subject. They went in for clinical testing for Tay-Sachs. This is a really important point that I would really like the Commission to think hard about, and this is the issue of trust in research. And I didn't hear that today, maybe again, the subgroup has discussed it. Ninety-nine percent of the public, and probably many people in this audience, maybe, don't realize that when you go in for clinical testing 20 years ago, that doesn't necessarily mean they're going to throw your sample out when they're finished with it. And 20 years later, that same Tay-Sachs testing sample that many of us may have given when we were pregnant or thinking about getting pregnant is now being used in studies for predispositions to cancer and other sorts of diseases. Now, is that good public policy? Maybe it is, but I would challenge us that we really need to educate the public that this is going on and to win their trust to support it. Because if not, there will be a backlash in the community, "Hey wait a minute—we didn't go in as a research subject." The individual that goes in as a research subject, that to me creates fewer issues because you can plan ahead and they've already assumed themselves to be a research subject. But many of these people did not. So that is the second issue that I think is very important to talk about. And then third, I think somebody mentioned this about keeping our conceptual framework in the context of protection—I think this was Chairman Shapiro. I think there is a real challenge here again, and that is under our existing

regulations, if we approve a protocol and we rely, as Alta Charo has said, perhaps on individual consent, there is nothing that speaks to telling the individual that there may be implications for their group, for their community. Now some people might argue, "What good is that?" If we get enough people to consent to it, it's going to have an implication with respect to group stigma or discrimination or whatever harm you're concerned about anyway. But if you're going to, in the end, decide that that's where you're going to place all your decisionmaking, then at least you could say that in addition to group benefit—which you do include when you're talking about why somebody should be in a research study, particularly a phase one research study has no direct benefit to them—you could also raise that maybe you need to include something about group or community harm. And it isn't just life insurance discrimination or employment discrimination or health insurance discrimination. To me, that's the easy one. We could try to pass laws to address all those things. We're doing okay in that area. I think these other issues, if you ask communities. If you ask the Native American community, and there is some research in that area, and we're now asking the Jewish community as well. They are not just discrimination issues, there are stigma issues independent of that. And that's very hard to get a grasp on. So those were the three main points that I wanted to raise and if anybody has any questions, I'd be happy to answer them.

DR. SHAPIRO: Thank you very much and thank you for coming. The issue you raise with respect to trust in research is something that we have discussed over time and is an important issue. Indeed, I saw Carol's graph, which dealt with future collected materials, and it distinguishes clinical and research subjects, in part, for that reason. Part because you face the problems that you have articulated. But the points you have made have been very helpful. Let's see if there are questions from members of the Commission. Alex?

PROFESSOR CAPRON: Karen, the position that you articulated here is one that some of us pushed three or four meetings ago. Trying to say that there was a difference—you put it in terms of trust, I would expand on that, but it's the same idea. Between knowing that your sample has been collected for research, rather than some kind of consent form where it was just in the background, that you're in there for a clinical purpose and they said "blah, blah, blah" and you weren't focused on that. It was very strongly argued to me by a lot of people here that I was wrong in that. The central point that made the strongest impression on me was that being a research subject is often very situation-dependent. And the notion that, let's say, you didn't go in when Tay-Sachs was a well established clinical entity in terms of the test being developed, but when Michael Kaback or others were first developing the test. And so at that point the sample was collected for research purposes, but the research was on something which you thought of as relevant to, as you said, the reproductive decisions you were going to be faced with and the safety for a child and so forth. And now the researcher is proposing to use it for the cancer research. Is there, would you say, for two next-door neighbors who, reading the newspaper, that samples were used by scientists at an anonymous research institution in Baltimore. That in order to use these Tay-Sachs samples to find out something about the prevalence of a cancer gene, would you say that the two people you would expect to have very different responses, the one who knew that her sample was taken in that early phase of the Tay-Sachs research program and the one who was taken a few years later when they came back to groups and said, "Would you like us to conduct a screening program at your community center or your temple," and the data were for "clinical purposes."

PROFESSOR ROTHENBERG: Well, I think in both situations, probably with sufficient amount of education and understanding, unless there was some strong commercial stuff going on, which I think Bernie made a good point is a whole separate issue, it might not matter. However, it does matter under existing regulations, doesn't it? Because in one situation, somebody came in. Whether their expectations were different or not, if they are coming in as a research subject, there are certain protocols—

PROFESSOR CAPRON: As I understand it—let's assume that the data have now been passed through a repository where they are not linked to any identifiers. So we have unidentified data and the person is doing exactly what David described. This is, to use Steve Holtzman, they only care about the meat. That is to say, they don't need clinical information; they just want to know in a population about whom we know one characteristic, that they are of Ashkenazi Jewish descent—that's all we know—what's the prevalence of this gene? And the researcher says, "Well, I have two pools. One with the people who came in originally for Tay-Sachs research screening and the others who came in for clinical screening. Do you want them both?" And the present cancer researcher says, "Yes, I'd like to have them both." And the result, I was convinced after all this, that the decision to have been "a research subject" in that first protocol, yes, does indicate some small willingness to help science to find answers. But it's not the answer to the question the present researcher has asked, and therefore that that commitment to research, that extra willingness to help research is so

attenuated that it probably doesn't really differentiate. And I would understand under present regulations that if that's unidentifiable information, existing samples, that you don't need consent from either of those. And I was asking if whether you, having raised the issue, really think that the two next-door neighbors when they open *The Washington Post* and read about this and speak to each other over the back fence, one of them is going to say, "I was shocked. I went in for clinical studies and now they've used it." The other one is going to say, "Oh, I wasn't bothered because I knew I was in a research protocol."

PROFESSOR ROTHENBERG: Well, I don't have a definitive answer, but I will say I'm in the middle of a quantitative study that is asking that very question. We're putting people in different situations, not only in the context of where they originally got their sample, but we're also asking them whether it matters as to what they then are studying. And I think that the stigma associated with cancer and the stigma associated with manic depression and the stigma associated with homosexuality—go down the list—are different for members of a community. Different communities may have different feelings about different issues. That's why some attempts now, prospectively, in the Jewish community to develop these panels of prenatal tests, clinically, are now including at the end a question—gets to Alta's concern about you would be stupid not to do this in the future—they'll say, "We would like to ask your permission to keep this blood sample for future studies that may have an impact on the Ashkenazi Jewish community—check yes or no." Okay. In the study that was done at NIH, I think it was 97 percent—and you could get this exactly from NCI - that checked "yes" that you could use those samples for future cancers. So the question really is in the clinical context if you ask that research question, would you get that percentage? I don't know—

PROFESSOR CAPRON: And that's not data that your study will show us.

PROFESSOR ROTHENBERG: No, ours is really an attitude study.

DR. SHAPIRO: Have you any other questions?

DR. MIIKE: I'm beginning to get a little impatient. We start rehashing everything all over again. I feel like I'm in a deposition where someone wants to ask every possible thing so we can extract certain things out of it. I'd like to get a little bit more focused. We've been going over these things over and over again and so I'd like to move on.

DR. SHAPIRO: I just want to remind us all we're in a public comment section, that's if you don't mind. In any case

DR. MIIKE: But the public comment is going on and on and on.

DR. SHAPIRO: Unless there are any other questions... Well, we in fact are not going to get back to eugenics because we're going to break for lunch. But we'll be back—let's try to reassemble in an hour.

DAY 2: AFTERNOON SESSION

FURTHER DISCUSSION OF HUMAN BIOLOGICAL MATERIALS REPORT -

Dr. Harold Shapiro, Dr. Thomas Murray and Commissioners

DR. SHAPIRO: In a few moments we're going to start with some cases that Steve was going to present. We've sent a scouting party out.

DR. MURRAY: My luncheon colleagues actually asked me to be sure that the chairs of this next session—we don't have that much time, it will be a bit over an hour—that we be quick with the whip and keep everybody on track. People have even authorized me to throw things at them if I felt that they were getting off the subject. Again, I hope in talking about the cases we can, in each case we can think three ways about it. Number one, does it fit in this conceptual scheme that we have and, if so, where. That's question number one. Question number two is what are the significant interests, ethical interests implicated, and question three is what are the protections that might be available and useful in that particular kind of case. Carol, did you want to quickly throw up the scheme again, just so we have it? Carol may also want to say a quick word about future impact.

DR. GREIDER: This is the outline that we had gone through this morning and this is dealing with material that is already stored in repositories. There is another issue that we, of course, have before us which is material that will be collected in the future with the future being tomorrow, essentially—not some indefinite date. That is, the future is not a very distant future. So this is exactly the same thing that you saw a minute ago with this whole half as stored material, identified/not identified being the same scheme that we just had. And this just breaks down future material into material that is collected in a clinical setting versus material that is collected in a research setting. And everything that follows is identical to the overhead that we went through this morning. That is, this breakdown—not identified and identified—is analogous to what had been broken here, not identified and identified. And then there are three subcategories in each of these. So if that breakdown is clear, what I'm going to do is to put up the more simple version so that we can talk about more clearly. So if my fellow Commissioners can just keep in mind that when we go through this in the future, we can just substitute instead of stored material, it would be future collected either clinical or future collected research. And then all of these subcategories will be the same.

DR. SHAPIRO: Steve, we would like to turn and consider some of the cases that you have proposed, particularly in light of what Tom said to present the cases as briefly as we can and then consider how it fits into such a schema as this and what the protections might be appropriate in those cases.

MR. HOLTZMAN: Just for the genesis of this, I went out and sent a note to people at the company to come back with examples of kinds of studies that we did or do and how these issues may be at stake. And Eric, these notes are a synopsis, I think, of your discussions with Lena Wu, who works in our technology licensing group. In terms of this schema, for what it's worth, I asked people to focus on this issue, this box, when you come down to it. The reasoning being that the least ethically problematic kind of case is this box—how do I do this? Because there may be issues of community identification, but certainly in terms of individual identification, they are not at stake. And certainly over here, where you've got actual identification of the individual, you're clearly going to have the most robust issues of consent involved and the highest levels of protection. So it always seemed to me that the cases we're really going to struggle with are here. Now, with respect to this, again not traceable—I take that to mean that it's provided to the investigator in such a manner that they don't know the individual. They have clinical information, not just the sample. It's clinical information but it's insufficient to identify the individual, and furthermore, the person in the pathology lab back here with the material can't tie that sample and clinical record that's been given to me, the investigator, to it as well. So when I come up with the research result, they can't tie it back either. So what we struggled with in the Subcommittee—at least in my understanding—was the need for samples provided in such a way with the associated clinical information such that additional longitudinal clinical information could come forward. And so the cases that are written up in front of you, I ask the investigators of the company to ask, "Why is that important?" And I think there are a few things that are illustrative in the examples and I think you all have these. The first point under Case A, this is from the person who actually runs our cardiovascular and neurosciences program, we never need to know that it's Jane Jones. So we couldn't

imagine a case in which we needed to have personal identifier information, but nevertheless, we needed to have the longitudinal information for the reasons cited in this case. And I think a couple of points that come out from this, and I think Eric summarized them, is the kinds of, what I'm going to call biochemical interrogations we do of these samples are multiple. They are not just mutational analyses. Much will be happening in the future in terms of looking at changes of gene expression, looking at protein changes and whatnot. And that the value of these or what we need is—if you imagine the sample comes in and we interrogate it, what we're interested in is with outcome. So if I look at these changes in various biochemical parameters, what does that mean in the long run? A good analogy would be something that we're doing. An example of this would be in the area of cervical cancer. I think people are familiar with Pap smears and whatnot. You get classification of Pap smears by pathological condition: CIN1, CIN2, CIN3. What one is ideally interested in is being able to get molecular markers that correlate with those changes and also are indicative of when those changes go on to a neoplasm or not. Zeke, I'm in your territory here. So that sort of drives to the issue of the longitudinal information requirement. Tom, you want me to address specifically, what now?

DR. MURRAY: Let's see, do we understand what box? Does everybody agree that goes in the—which box does it go in?

MR. HOLTZMAN: Right. From our perspective, we want it to be in this box, all right? We never need to walk back to the actual—we, from our perspective, the investigator's—never need to know who the individual is. If there's a way in which the information can come forward without knowing who the individual is, that's fine; that's better. The motivations for going back therefore, are not having to do with the investigation or the research. They are more motivated by issues that people have expressed that are clinical reasons, such as you find out that there's been a misdiagnosis and from a human clinical concern, you want to be able to go back. But that's not constitutive of the research enterprise. Alta, you seem to be about to ask a question.

PROFESSOR CHARO: The issue is never going to be what the researcher needs or wants. The issue is going to be whether the possibility exists for the walk-back because the possibility existing means that an ethical dilemma could arise in the future. So I want to understand that what you're suggesting is that we focus here on a scenario in which we have this magic encryption technique that indeed does allow information to flow to the researcher for longitudinal study purposes. But that through this magic encryption it's not possible. It's not only that the researcher doesn't want to, but that it's not possible for it to walk back, correct?

MR. HOLTZMAN: And again, I think at the last meeting I raised this issue. When I look at how the Subcommittee thought about this, why we moved to this notion of being what we used to call "used in an anonymous fashion," the question was if that meant this box, then you couldn't get longitudinal information by definition. If you could get longitudinal information were you, by definition, cast into this box?

PROFESSOR CHARO: What I'm asking is for the purpose of the scenario that we are going to discuss, can you tell us, are we going to premise the discussion on the idea that there has been an encryption scheme developed that does, in fact, allow for a one direction only flow of information from the repository to the investigator.

MR. HOLTZMAN: Okay. What I can say in terms of our studies now being conducted, in terms of an encryption scheme of the type where it's a computer doing it, the answer is "no." We conduct our studies in such a way that there is the possibility of walk-back as well, given the techniques of encryption that we are using.

PROFESSOR CHARO: So which scenario do you want us to discuss, Tom?

MR. HOLTZMAN: We don't have access at this point, the way we effectively make it not reasonable/feasible to walk back is that effectively there are firewalls built. But those firewalls can be broken. It's not an encryption scheme which is unbreakable other than by having to do calculations for longer than our lifetimes.

DR. SHAPIRO: The firewalls are only designed to withstand heat at a certain level for a certain time. So now may not be so bad. It takes some effort to get over, to you can get over there eventually.

DR. MURRAY: So what I'm hearing is that you have—I'm not sure what I'm hearing. Are we in the encrypted feed-forward and that's it, or the encrypted feed-forward and walk-back? What box?

PROFESSOR CHARO: Steve, if I may? Your current situation is one in which you are at encrypted feed-forward and walk-back. That's what's possible, even if that's not what you intend to do. Just for the sake of clarity, it's

worth noting that current regulations have something to say about the situation. Current regulations say that there is a human subject involved, that this is a protocol that is not exempt from IRB review. And that the IRB, therefore, has to review the protocol for its risks and benefits, etc. That consent from the original tissue donor is ordinarily going to be required unless you meet the four criteria for the waiver of consent that were laid out in chapter 4, when Melissa was writing up the regs. And minimal risk is one of those criteria, but another crucial one is that it be impracticable to reach the tissue donor. So under current regulations, which we could choose to change but we should at least know what they say. If it's possible to go back to the tissue donor, we have to in this situation. That is the way the current regulatory system works. You may, nonetheless, be able to get expedited review under the IRB if it's minimal risk, which it may very well be in many situations, but you do have to get consent from the donor if there is a feed-forward and walk-back. It's just kind of the way it is.

PROFESSOR CAPRON: Could I add one thing there, Alta? Aren't we talking about here someone who is currently, in every real sense, a participant in a study? This is a person who is going into the hospital and his or her clinical data is being converted into research data and fed forward to a person conducting research. There is, obviously, no difficulty in contacting that person. You know who they are, they are coming into your hospital, and you're providing that information to a researcher.

PROFESSOR CHARO: I'm not disagreeing with you, Alex.

PROFESSOR CAPRON: Okay. I just want to be clear that it isn't—I don't think we get to the point that you were getting where you would say, "Is this a person where you get a waiver of the consent requirement, because this is stored data, although it's identifiable—are there reasons to waive because of difficulty?" How can there be a difficulty?

PROFESSOR CHARO: I'm not sure. But my purpose was entirely simply to set the stage for what is currently required so that when we discuss what we would like the protections to be, we understand if we're talking about additional things for IRBs to do or an actual change. Because they can't violate the current rules of impunity.

PROFESSOR CAPRON: I agree with you. That's why I thought these discussions were always going to be moving out of the boxes to the decision points that follow below the boxes. Which is where the real action is.

DR. LO: We have two candidate boxes and sort of an example that might be either—and I thought we wanted to push ahead and say in each of these boxes, what are the interests at stake and flowing from that, what are the recommendations?

DR. SHAPIRO: I agree, and let's just assume for our discussion coming up at the bottom right-hand corner there. So let's just assume to top that out. Before we do that, Zeke has a—

DR. EMANUEL: I have three or four examples. I don't know if they would be helpful, I could try to thumbnail them. All of which had been distributed in previous notebooks three or four months ago but they may be worth reminding. The abstracts for almost all of these papers and many other kinds of uses have been distributed in prior notebooks. One is this case of looking at the tumor angiogenesis factor in breast cancer samples. Folkman thought he had an antibody that could identify tumors that caused blood vessels to arise. Went to the Brigham, got 104 slides of women who had been treated 5 to 10 years previous to the date he initiated this study. They were gotten with the names scratched out, but with clinical information. So he knows who relapsed, who died, who has had no problem, what treatments they received. Did his study, I presume without informed consent—I haven't asked him, but it doesn't suggest. In that case, I think it certainly could be encrypted feed-forward. There was no attempt that I know of to walk backwards and identify the people with the results.

MR. HOLTZMAN: Let's not confuse whether there was an attempt to walk back with whether—

DR. EMANUEL: There certainly, if he ripped up the sheet of paper—I don't know how it was done. But here's an example, okay? Carol asked, "Why is it coded, not traceable? Okay, so it's coded, not traceable. Here's another example. The Nurse's Health Study, there was a controversy over silicone implants. The Nurse's Health Study had x thousands of women, they had data, they had never intended, as best as I can tell in their informed consent, to correlate outcomes with the silicone implants. They, however, went back into their database and correlated. These women who had silicone implants have a higher rate of rheumatoid arthritis and other health problems. And that was done in a research setting at a one-time standpoint. Another case of exactly that kind of study was done at the Mayo Clinic with women who had come in for clinical care, not as part of a research study.

DR. COX: Where was that last one, Zeke?

DR. EMANUEL: That's the Nurses' Health Study—

DR. COX: Where, in terms of our—

DR. EMANUEL: I think that is traceable because I think it's encrypted feed-forward.

DR. COX: They were accumulating current information?

DR. EMANUEL: They kept sending out to the women, going into a computer into a database, but no names attached to it. Sorry, thanks, David. And the last example which I bring up because it's a similar kind of study, but it's the Mayo Clinic going through its wonderful clinical database of people who have been treated at the site for clinical reasons, for breast implants. Same issue, they went to their clinical records and looked through, got all the women in Olmstead County who had gotten breast implants and then looked in their medical records to see what the outcomes were. And that case, again—it's not specified in the paper exactly what they did, but they could have done it, I think, encrypted feed-forward or encrypted and not walked back. Or they could have done it "coded, not traceable" by just ripping up the sheets after they had abstracted the information. And that's in a clinical setting.

PROFESSOR CAPRON: But with all of these, though, as the Chairman reminded us yesterday, the amount of clinical data may be an alternative way of identifying some. I mean, how many black women aged 54 are there in Olmstead County who had breast implants? There may be two and you may have them both in your study. So sometimes—add on the factors, "with six children." Whatever the factors are, you say "well, this is so and so."

DR. EMANUEL: I think the norm with 10,000, 15,000 or even 104 patients out of the last 50,000 that you've done—we shouldn't take that example because I think that's a pretty extreme case. That's not the norm, as it were.

DR. SHAPIRO: And then I really want to get back, as Bernie suggested, to deciding we're in one box here for the purpose of our discussion and just look at the protections or interests and therefore protections we want to provide.

MR. HOLTZMAN: I think it introduces, to this last little point of Alex's, it introduces conceptual clarity to ask whether the information in the hands of the researcher is sufficient to provide identification of the individual. A name usually is, all right? Sometimes there is a small enough population and sufficient clinical—it will be. So that's the decision. So I think the question you were raising, Alta, when we initiate these as research studies, full-blown informed consent is involved. I think what the Commission needs to be thinking about is where things are going. More and more of these studies, your paradigm of the family study is irrelevant in genetics. Where we're going is a situation where we're going to have very dense biochemical markers, be they the DNA, RNA, protein and all that. Where more and more of what you want to do is be going into broad populations. Which means by definition, what you're doing is you're going to the pathology labs. And so the pathology labs know right now that they are going to be accumulating samples which are likely to be used in research. They always knew it, but they know it even more now. So when we find ourselves working with individuals now in labs, more and more we're sending up tissue banking relationships with pathology centers. And the difficulty you run into is that the kind of robust consents we have traditionally used in a research study don't really work in the context of the pathology lab that is collecting it in the clinical setting. And yet, we know we are going to be conducting research. I think that's the issue one is struggling with. It is something you were raising, Alta. If you go to the chart which OPRR has handed out, the first question is are you dealing with human subject research? Well, when we have got a sample from the pathology lab as opposed to in a research context, there is no intervention or interaction that wouldn't have happened. We don't receive information that proves sufficient to be able to identify the individual, hence the understanding was that it was not human subjects research. At least that's how the research institutions interpret that. I don't know if that's consistent. Now the next question is if there was no interaction or intervention and there is not information sufficient to provide identification, but there is a continual accrual of additional clinical information going forward, are you still outside of human subjects research or have you somehow come into it?

PROFESSOR CHARO: It probably makes sense to save for a little bit later the kind of detailed step-through on the regs. But I would heartily endorse the notion of simply settling for the moment on the case that Steve presented, which was in fact one in which information can flow forward. And regardless of people's original intentions, is capable of flowing backward and identifying the interests that people have, both in being protected from harm and in receiving potential benefits.

DR. SHAPIRO: I agree. I think we should carry forward as if we're in the bottom right-hand corner there and identify the interests and protection we're interested in. And then we'll worry about the others as we go along. Let's see what people have to say about studies that are characterized in that fashion, such as Steve's example. I think it's an interesting example.

PROFESSOR CAPRON: One interest that I will put on the table—aren't we at that point? Okay. What Buchanan talked about is being told that you're in a research project and being able to say "yes" or "no" to being a subject independent of whether other people looking at this would say that you're at high risk of physical or financial or social harm from it. Just the notion of being a participant in something that is viewed as giving something; "I'm willing to contribute to research." That is an interest. Alan suggests it in here, but he doesn't fully, it seems to me, address that. One thing he does is to move very quickly to a notion; "are you saying that your tissue is your property?" And he correctly notes that the Moore case said no, property is not the right way to analyze it and put it in terms of the fiduciary obligation of the investigator, who was also the physician, to inform you that he had an interest in this case, a pecuniary interest that might lead him, as your physician, to do something. I think that's fine for describing the Moore case. I don't think it helps us that much when we're talking about samples that were collected by someone who was in a physician relationship and who was not influenced. And there's no reason to think that they were influenced because they wanted to contribute to a databank and get your spleen into the databank. They only wanted to treat you. But the pathologist who was taking it and looking at the spleen and then giving back some clinical information, was going to hold onto it. I think the present, this Chart 1 that Steve just reminded us about, addresses that because the question, for me, has that sense of is the clinical decision being influenced? And the answer may be "no," but even when you get to know, then there's still the further question that can lead you back into a recognition that a human subject's interests are involved. Will there be identifiable data of the type that would come with a flow-through that would make you a subject? And then you're back with a "yes" answer to that question, we're back in the human subjects thing. I want to try and—I can point you to, I think it's page 49 of Buchanan's thing—where he comes back because he's rehearsing three interests which he says might be important. And he dismisses this one by, I think, mistakenly going back and saying, "Well, we wouldn't think that the subject has any right, property right in the sense of a claim to profit from the research." And I would agree. But that, to me, does not exhaust the issue. I don't have a property right in terms of profiting because I have some kind of property interest over my ancestors' graves and no commercial interest. But I have a property interest in keeping you from invading that space. Yes, I have a property right. The reason I can keep you from coming onto that or disturbing that is not because I'm deriving any profit or that I intend to keep it and sell it to someone, and that's one reason we have property—property is a bundle in interest. And here it's an interest of not having something used over which you have an interest. The conclusion from all this—I know Eric has pressed informally a couple of times saying, "What's really bothering people about all this" as though he was going to approach this like Dr. Freud or something. I don't know what's really bothering me about this, Eric, but I do—no, no, no, no. I think Buchanan is writing and speaking in terms of interests other than simply the avoidance of harm. But we really are avoiding a harm. We talk about a right that allows you to assert yourself against that. Here we can talk in terms of interest. One of your interests is in not being used because a basic understanding of what it means to be an agent with free will is that you are involved with other people at your choice and not simply at their choice. We seem to have resolved, and the present regulations have resolved that by saying if it's just your tissue and nothing about you is attached to it, you are not involved and therefore that interest is not implicated. That seems to be the answer. That seems to be the present answer. I think we should ask, "Is that a full and accurate representation, given the kinds of uses that could now arise?" But overall, we think that's the case. I can recognize, however, that if I had had a tissue sample removed and someone was now going to be developing a genetic engineering technique that I objected to—or if I were against ever having an abortion done, an abortion technique—the fact that they had access to it might still offend me. Now the fact that I don't know that it's mine anymore and that it's anonymous and it could be somebody else's greatly diminishes that. And it may be such an attenuated interest and it may be so difficult to allow me to protect it, as to those things that are already stored, that we as a society are going to resolve that by saying—and that's what Buchanan tries to do to some of these interests. It's too small to erect barriers to its use. But it still does not seem to me incoherent to describe that as an interest, and an interest which may even be offended in a certain sense. So if we could say to the person, "Well, we know that this wonderful breakthrough and something which you abhor was made with your cells which were particularly useful for that," they would say, "Oh, my God!" It's like a question of a Jehovah's Witness child who is given a blood transfusion, and because we believe in saving the child's life, and the child later looks at that and says "I'm now damaged forever in my own belief system." We weighed that person's life against that interest and we chose their life. But we have to recognize that there was another interest which we didn't

give as much weight to, which we had to override.

DR. MIIKE: If it were feces or urine that was the material?

PROFESSOR CAPRON: If it were material for me—it's material for me. It's that participation. And I'm not—please, understand me. I'm not saying that I would resolve it differently than the present Federal rules do. The present Federal rules say that material from a person which is no longer identifiable with them, the answer, again on Chart 1—no, no, 45 CFR 46 does not apply. We're not talking about something where the interest of the individual is strongly enough identified. I think, in fact, as we work all this through that I'm going to say that we probably don't have to change that. I'm just saying that we don't get there because there are no interests. We get there because we're weighing the difficulty and so forth.

DR. MESLIN: In the interest of disclosure, I just wanted to remind those who are observing the proceedings that we announced at the previous meeting that Professor Alan Buchanan from the University of Wisconsin had been contracted to write a commissioned paper for the Commission on the subject, portions of which you've been hearing. He was unable to come to today's meeting, but the second draft of his commissioned paper has been distributed to the Commissioners. I am sorry that you were not able to get it. It will be available on our web site and will be available to you, as I hope many of our materials will be following yesterday's presentation. So forgive the conversation about a paper which many of the Commissioners have read, but hasn't been formally presented to the Commission by its author, Professor Buchanan. So I hope you'll treat that in the spirit with which it's intended. We apologize for that.

DR. SHAPIRO: Right now we're trying to think of interests and what protections are needed, if any. Eric?

DR. CASSELL: I'm trying to stay out of this today, but we're interested in something that ought to become performative. Whether what we're about to impose is equal to the kinds of things that Alex described or is equal to the kinds of things that Buchanan talks about when he talks about a descriptive problem with a group. And I must say that I started out this trek through the Sahara more convinced that they were a problem requiring rather strict control than I am now. As you go on, I've become less and less convinced that this matters enough to have, to impose big problems for the research community. I understand that there are venal people everywhere. I understand that there are untrustworthy people everywhere and somebody may turn around and screw you at any time. That is not the issue, nor is the issue whether some of the harms cannot be prevented in other ways. If stereotypes are used negatively, we don't stop that by labeling tissue in some way. We stop that at the point the harm takes place. So I must say that all of you, if that was your intention, have convinced me that we have to be very careful before we erect barriers that are much greater than the interests that are injured.

DR. LO: I want to follow on these last couple of comments, because Alex has put his finger on something that I've been troubled with. I think an awful lot depends on the nature of the study being proposed. That's not captured by this schema we have. And I think in the back of our heads we hear Dave and Steve and others sort of say, "These are the kinds of studies that are sort of cutting-edge molecular genetics that will lead to improved diagnosis and cure." And everybody says, "Yeah, that's a good thing—let's go for it." I think there are other types of research that we need to bear in mind. In the other half of our Subcommittee, the Committee on Decisionally-impaired Subjects, we've had a lot of examples of research that you really question the premises of the research and they're the exactly the kind of research that Alex described as—I might well feel that, not just I as an individual, but many thoughtful members of society might feel offended that they somehow participated unknowingly in that research. Whether it's by having a stored tissue sample used or whatever. And I think we really have to put it in a context of, there's been research on behavioral genetics which has been very pernicious, which often isn't peer reviewed. I think that somehow we've got to take into account that that's not just a theoretical possibility; it's something that's happened historically. If you look at the IOM report that's still under review because it's so controversial and you look at the types of studies being done today, I think a lot of people would say, "Why are we doing this research?" It's really sort of political statements under the guise of science and I think many people would say that bothers them even more than if they happen to have a personal belief about not wanting to participate in research that have commercialization or fertility implications or whatever. And I think that it also intersects with themes that we talked about this morning that have to do with certain communities that have traditionally been discriminated against. The study that we that we were just given today about how fenfluramine challenges and siblings of kids who have behavioral problems. And there's a lot of behavioral genetics that's—there's a whole chapter of the IOM report that talks about what they call antisocial behavior, which is everything from truancy to setting fires to a criminal record. I would disagree with Alex and I think this may be something more important in the

context of certain types of studies that historically have been extremely problematic. Somehow before we say that there's an existing sort of way of approaching this that says it's not really that big an issue, it would be awfully hard to erect safeguards that wouldn't cause a lot of detrimental side effects. I think we need to sort of think through—I guess what I'm saying is the worst case of research that many people would find troubling, not just a few people with certain idiosyncratic beliefs.

DR. MURRAY: If I heard Bernie correctly, you're talking about a kind of harm to an interest that Buchanan describes as avoiding use of biological samples that the source regards as impermissible per se. Does that sound right to you?

DR. LO: To follow up on Alex, even if I'm not directly identified as being in the study, even if I may not even—

DR. MURRAY: That's how he intends it.

DR. LO: What page are you on?

DR. MURRAY: My pagination is 9 if you print it single space.

DR. LO: I just want to say that I thought Alan didn't give it as much weight or consideration as I would want to in the context of certain types of—

DR. MURRAY: That's the interest. We need to think about what sort of then protection we might afford that particular interest. One conclusion is it's a cognizable interest, we understand that. But it's going to be some rare or so insignificant that we're not going to build a policy around it—that's one option. One could imagine a range of options. Another option is to say, "Look, this is significant, perhaps relatively rare and maybe what we need to do is not establish like a whole different category for it, but place something in the review process in which this question at least gets raised by, say, an IRB." Is it plausible that some of the people whose samples might be involved in this process would think it impermissible per se? I just want to sketch out that there are a variety of ways that we might respond to some policy—

PROFESSOR CAPRON: And we do that already vis-a-vis consent, but there are certain kinds of studies which involve sensitive matters where the waivers cannot be used in the same way. And so your notion that you get to this and you still have another question you ask and you only get to know, in terms that you don't have to worry about the regulations if you're not in that category. And if you are, then you need some review.

DR. COX: I'm talking about the same interests that Alex talked about and that Bernie is talking about. And these are interests from the perspective of the person or the research subject, let's just call them that. The person from whom the tissue has come. For me—and I'd like to come to Tom's ways of actually, what are the protections in place—I'd like to say that I see this very much a continuum. Not in the way that Bernie was talking about, although I understand what you meant, Bernie, in terms of the actual subject matter of the research. But I want to look at this as a continuum in the amount of information that the researcher has about me. Whether or not it can be used to uniquely identify me. And to me, that's the specific interest because if somebody has some clinical information from me, like a small amount, like basically what my blood type is. But they don't know my name. I've got to tell you—I'm not too worried about it. But now they know my blood type and they know three other pieces of clinical information. Well, it's actually getting a little bit more relevant to me.

DR. MURRAY: But they have no way of knowing whom you are.

DR. COX: Exactly. They don't know who I am, but the information that they have becomes more interesting to me personally. That's the point. And as it gets more and more information, it becomes more and more interesting to me personally, because it's directly related to me personally. So why I'm doing this interest is because for me, it's a spectrum in terms of the protections that I would like to have. So the interest then, is that I feel more and more. The more information that the researcher has about me, whether they know my name or not, the more I feel that I should be able to be part of the process.

DR. MURRAY: David, I think you're a very interesting person, actually, but I have to say that I don't know that you have any more interest in controlling—say again, it goes forward. It's in a box

DR. COX: We're still in the same box, okay. Encrypted, coded, forwards and backwards. That's the box that

we're in, I thought.

DR. MURRAY: So they don't know your name now, but they could find out your name.

DR. COX: And the point that I'm making now, no longer talking about the research subject, but talking about a researcher, me being the researcher. The more specific information I have about any sample, the less comfortable I get without making sure that person is a party to my research. And that in that context, one can have protections that are sliding protections. It's not just whether you have some information or no information, it's how much information and it's more than just whether that information provides a unique identifier or not.

DR. EMANUEL: Are we talking about the future and that box?

DR. COX: I'm talking about today.

PROFESSOR CAPRON: A presently stored sample with new incoming information—

DR. COX: I'm talking about today.

PROFESSOR CAPRON: New incoming information where you can go back to the specific person.

DR. COX: That's correct. Because it's possible. And that's that box, that's what I thought we were talking about. Those are the interests. So I'm really trying to stick very specifically to your charge and the protections are ones for me that would be on a sliding scale. So if we have any strict cut-point, I'm not a happy camper because for me it depends on how much information is there.

DR. CASSELL: So we ought to concentrate our attention on the education of the investigator, not on the specialist. Because actually it's how you came to see this that changes it rather than that specimen per se.

PROFESSOR CAPRON: Every investigator in the country should have to sit through three of these meetings.

DR. SHAPIRO: Okay. We have a number of people who want to speak. Alta and Larry, and then Zeke.

PROFESSOR CHARO: I'd like to speak directly to what's unique about that box which is the walk-back possibility. It is not about the researcher's intentions; it's about the fact that things arise in which suddenly there's a surprising...classic division here which said I have a very protectionist tendency. I've always been uncomfortable with the speed with which we have accepted the notion of enrollment for minimal-risk experiments, whether or not they have some potential benefit, and so although it appears in Appendix 2 with the requirements that we're suggesting in the actual written recommendations, it's not laid out. And for the purpose of eliciting public comment, I'd appreciate it if we did that, especially because the requirements are the same in both cases, which is no dissent, and there is room here possibly, especially in the area of minimal risk but no potential benefit, which is where it's particularly difficult to justify, for something slightly different, like the need for assent as opposed to dissent. I'd like to just lay that out.

On the greater-than-minimal-risk categories, no comments on Recommendation 8, which is the one that involves potentially beneficial research. On category 9, which is the one that Laurie was concerned about, that's greater than minimal risk, not potentially beneficial. Two things: First, I take seriously the assertion that I heard several times that a very large number of people who are in these populations in fact have the capacity to consent and that therefore is not clear to me that something that says, "Only with their consent can they be enrolled in greater-than-minimal-risk research that's non-therapeutic," will necessarily shut down research in this area. If indeed it's true that many of them can consent, there will be a pool of people from which to draw for research subjects. Since the research is by definition not beneficial, it's no wrong to them personally in terms of their interests in getting experimental therapies, and we will, in addition, be able to see benefits for the population as a whole, which is why I'm still comfortable with a protectionist attitude.

On the other hand—and this is related to Larry's thing where, I'm sorry, I was getting our side of the table out of order before—what I recall from that exchange, and my memory easily could be wrong as well, I recall that we were suggesting that for greater than minimal risk, not potentially beneficial, you would need either informed consent or an advanced directive for research that had been made out at an earlier time when the person was competent to do so, and that this would somewhat expand the pool of potential research subjects for this category of research. I could be remembering it wrong, but that would seem to me to be something worth considering for this category.

DR. MORENO: I think that what people were telling me was that what we had been thinking of as an advanced directive was a semantic error and that, in fact, what we're really talking about is planning...in the informed consent context for a specific study or a kind of study. So, that's why the term "advanced directive" would seem to people to be inappropriately hauled in from the clinical context and so forth got taken out.

PROFESSOR CHARO: Right, okay. But some provision for somebody to give prospective consent...to have somebody else make the decision to enroll them, even in non-beneficial stuff, is on the table? Yes?

DR. MORENO: I think—I think it's in the rubric here.

MS. FLYNN: I didn't see it and it's part of my concern that I think we've created a box and it's very hard to get out of it.

PROFESSOR CHARO: Right. But, remember, though, that if it's true most—that a large number of these people are capable of consent, that we have still not shut down research in this area, right?

MS. FLYNN: Yes and no. That large numbers of people are capable of consent much of the time. But the kind of research that is most critical, the kind of research where we want to look at individuals, do PET scans—I'm talking about the problem we created when we took away the category of minor-increase-over-minimal risk and made everything a big risk. When we want to do PET scans on people who are actively psychotic, it's really good to know what the brain looks like and how it's functioning and what's working and not when it's actively psychotic. It could help us a great deal. I don't see how we can do that. We cannot get their consent when they're actively psychotic.

PROFESSOR CAPRON: That's true. Advanced planning.

MS. FLYNN: That's nice for lawyers to talk about, but the reality is that almost nobody—we know and you all pointed out in earlier discussions, in other parts of medicine we're not seeing this. There are lots and lots of challenges to it. It's going to be very difficult to get it. And for a population that is characterized by Medicaid eligibility, long-term poverty, it's going to be hard for us to imagine—I mean, members of my organization might be able to get with their relatives, but the kinds of research that we need, we're not going to be able to get the very people who could benefit the most, and I think it's not going to happen.

PROFESSOR CHARO: I'm just going to give you the last thing on my list so that I can move the chart over to the next person.

MS. FLYNN: I don't mean immediate benefits. I mean as a—.

PROFESSOR CHARO: The last thing on my list so I can give up my turn to somebody else. Appendix 1 in your definitions, "necessary use"—this is page 148—"necessary use" means that the IRB should not approve research when such research can be done with other subjects. Just to remind you, something that turned up that you'll find in the transcript—Tom Murray noted that there may be circumstances where people who have these kinds of disorders also have other kinds of conditions; for example, an advanced cancer for which they would very much like to be enrolled in research and that we need to craft this language, and this is a mea culpa because Eric actually asked me to help with this and I couldn't remember what he wanted me to write about—I never wrote anything. But we need to somehow craft into this that when there is a serious condition for which enrollment would be potentially beneficial and existing therapies are not adequate, that we shouldn't be excluding people just because we have some problem with the—just because we tried to set up a presumption against the enrollment of people.

DR. MORENO: I think this is what you and I had our E-mail conversation about. What I don't understand about that suggestion is, wouldn't those people be covered under a compassionate-use exception? You don't want them in the research project. You don't want them to be counted in the numbers.

PROFESSOR CAPRON: You want to be able to give them the benefit but not exploit their decision-making problems to make them research subjects.

PROFESSOR CHARO: That's actually a good solution. It didn't come up at the discussion in Los Angeles.

DR. SHAPIRO: Larry, you're next.

DR. MIIKE: I don't want anybody to comment on my comments. I know it's hard, but I'm just going to say my main issue is around this prohibition without informed consent, without beneficial research, and my problem is as follows: I sent an E-mail message, I think in January, raising this issue, and I said that if you read the body of the report it had a whole range of other safeguards that were not considered before we reached this rather drastic conclusion and one of them was the Secretary's type of thing. But there are more than that. Number one, on the consent side, we just had a discussion yesterday and today that advanced the records of general consent documents, or their general consent. They're not specific. So I don't see how an advanced directive can replace the specific consent around a specific project. So I would not agree that advanced directives help by making it more available. I don't think it's the same thing as informed consent. If we stick to the issue about benefits, what we have is the following: There is the discussion about direct benefits and indirect benefits, but there is no parallel statement in this recommendation about what benefits we're talking about. And, if we're going to be talking about benefits—if we keep it this way and I want direct benefits that arise specifically around the intervention and not this thing about they get free medical care, etc., etc., then, the other part is that this is going to lead to disingenuous statements. They are going to try to find the benefit rather than face the issue directly about how we have safeguards. So, it's too much of a slippery area for me and I would rather have a very tightly crafted allowance with enough safeguards in there. But there are lots of things around this particular area, which I think can be done; for example, there are other statements that you'll not use such a person if other classes of people can be used in those particular—so, it seems to me that this will be such a narrow exception, and it will be so scrutinized, and I would rather have that than have a blanket prohibition.

My last comment is on the recommendation about State legislation. What I worry about that is that we've got 50 States, and if you start having the standards of the State legislative statutorily defined surrogate decision maker or someone that stands in place, it'll place in turmoil those areas where we do not have a clear State statute, and this is such a narrow, small area that I don't think too many States are going to even bother with a stand-in person, particularly for the research area in an advanced directive site. So, I think that that might sound good to offer up, but it's just going to complicate the situation and may actually—it may actually impede the use of a surrogate or decision maker in this particular area that's, I believe, on page 140—140, so it's not going to improve the situation; it's going to make it worse.

DR. SHAPIRO: Larry, thank you. Let me make a comment that I wanted to make before. You will, of course, have the transcript of the meeting and that'll be very helpful for those of us who are going to continue drafting. It would be even more help for any issues on which people quite strongly if they would try to submit some language and where you think it might help and so on that really would enable us to reflect your review much more faithfully and not allow us, as we probably sometimes do, to forget them or don't completely take account of them. So, if we come across views that are mutually inconsistent, we'll have to argue those out at a meeting. But, that would really be extraordinarily helpful because there have been very thoughtful things said here today—I'm sure there will be more thoughtful things. And if any one of you feels strongly about them, which I think you do, please give us a chance and—to reflect that feeling, and if you put it in writing that'll be a big help, although we will look—we'll use the transcript to help us. The next person I have on the list is Jim.

DR. CHILDRESS: I very much appreciate the kinds of concerns that Laurie's raised. I think this draft actually does a pretty good job at reducing the number of external people involved, and let me just note what is required or what we say may be recommended by IRBs. Obviously, the competence assessment is one where we involve someone. But we understand the legally authorized representative basically to be legal recognition of the kinds of parties who are already usually the ones who'd be involved and the kinds of ones who Laurie's most concerned about. And then for the independent health care professional monitor, we require that in greater-than-minimal-risk nonpotentially beneficial research and then say only that the IRB may—*may*—not *required to*, but may require it in the potentially beneficial research area where there's greater than minimal risk. And, we say the IRB *may* require a consent monitor. So I'm not sure that we end up with the kind of rigid requirement here of a variety of external parties that would go very far beyond what Laurie's proposal already included. But I'm sure there's still room for a fair amount of debate about that, and I agree with Harold—I very much hope that people will get their views in so that we can take them into account, even perhaps present alternative wording in the next draft so that people can make some choice then about which way they want to go.

DR. SHAPIRO: Thank you. Trish.

MS. BACKLAR: I'm hoping that we could have a discussion about minimal—that we could start to clarify what we mean about minimal risk, because I think there's a lot of discussion about what we're putting in place that we can't get to until we have some agreement as a group on what we're going to mean as minimal risk and how we're going to look at what happens when it's whatever it is above minimal risk.

DR. SHAPIRO: Okay. We'll try to get back to that as soon as we can. Eric, have you—still have something you want to say? No. Alex?

PROFESSOR CAPRON: Trying to focus on the language of the report, Arturo raised an issue which we've looked at several times in the past, and he raised it to Laurie and I was very confused by the answer. And I'm not trying to encourage the dialogues that apparently are not a good idea among Commissioners talking to each other, but the language that we use in the report, now, is "persons with disorders that affects decision making capacity." That's the definition. I don't now from this discussion whether either Arturo or Laurie thinks that that's the wrong category. I don't know whether Eric, by his example of the fact that mental conditions are not the only thing that affects decision-making capacity, means to say we shouldn't use that language because medical conditions are in that category. It seems to me that that is the absolute trigger of the entire report, and if we are not clear about that then it's not just recommendation no. 3 where that language is, but throughout—after the last meeting I sent in a lot of material to Jonathan in which I tried to synthesize what I thought was the discussion and most of that is reflected here in this latest draft. And, we used that language. That's the language that triggers having an IRB with diverse membership. Can have a decision about that? I don't understand, since Laurie's comments followed my last comments, whether she thinks that I was in the category with the person who was saying that we shouldn't listen to mental patients who say this is the decision I want to come to, or she thought Eric was taking that position. I simply wanted to be clear that any time that we don't listen to a person and we say either your capacity isn't there or we don't like the judgment you've made, we're overriding it, and we may override it in a way which is very defensible. It may even be necessary to do so. But let's be clear that is what we're doing. And let's be clear the interests that are given up, including, Laurie, as you say, a lot of people who are offended. Patients in that category say, "I should be able to make—I can make my decisions. Why are you stepping in for me?" Among my schizophrenic relatives it is often the notion that the relatives are the last people they want to have involved. They are the relatives of the people they distrust the most compared to others. So, you're following that with the comment about the value of having family decision makers in the process. I suppose, in the ordinary course, if I'm going in to see my doctor about something and I bring my wife along, that's my choice to do so. But if I don't bring my wife along, no one says I have to have my wife there to help me make the decision. So, I—I'm not clear whether this is a comment about something that may be helpful if the patient wants it, or something that an IRB should require or want to have.

On the legally authorized representative, I would ask that we would have staff very quickly and easily, themselves or talking to someone like Judy or somebody who's followed this, just to tell us what is the status now of State laws. The common-law tradition was that next-of-kin stepped in to make medical decisions. There was in fact no actual common-law decision making basis—I mean, the decisions, the judicial decisions—basis for that. It was as dictums set by judges. Well, of course you reveal the information and get the consent of the next of kin, but it was never the issue in cases. It was just a practice that everybody did. Now, many states—I don't know if it's roughly thirty-some today, and that's what you could advise on—have adopted family decisionmaking statutes of one sort or another where, for mostly growing out of the end-of-life care issues, they actually say, "Here's the priority order of people who are supposed to decide." If most all States have done that, then the phrase "legally authorized representative" is defined by those statutes, and we're just meshing with State laws. I don't think this is an area—and I don't know if Larry meant to say this—is where we'd have Federal preemption and we would say that the right—. So we're going to be stuck with State laws, and all our language in here now says, with which I agree, is the State legislatures should attend to this issue. Now, many of them won't read this report, but if there are only two or three states that haven't addressed it, maybe it's not a big issue.

Finally, I don't think that anything we're doing in here prohibits research. We had a recommendation to prohibit cloning. That was a recommendation. A time-limited moratorium. There's nothing in here that says subjects should not be used if they have mental disorders or certain categories of research should never be done. We have a process by which the subjects, the researchers, and the IRBs, and maybe the Secretary or maybe somebody else would

be involved in deciding who should be in that research and when it can go forward. We don't have prohibitions, and I think unless there's language in here that says we have a prohibition, I don't think we should attack the report for instituting a prohibition.

DR. SHAPIRO: Thank you. Laurie, and then I want to come back to one or two of the comments Alex made, then Larry and Trish.

MS. FLYNN: I may actually have to have a back-and-forth with Alex for a minute, just so I can understand what he's saying.

DR. SHAPIRO: What I said was not that we *shouldn't* do it, but if you could avoid it whenever you got a chance it would be helpful—but not *you shouldn't* if it's necessary.

MS. FLYNN: Then we can do more later. You made some reference to the concern about family and whether or not family should automatically be involved in referencing the—. Very often individuals with schizophrenia are suspicious of their family. That's the last person they want involved. And I would simply point out (a) that's characteristic of the disorder. It's quite painful for families, but it's quite characteristic of the disorder and one needs to understand it for what it is. It's a symptom of the disorder, particularly when it's not treated or not well treated. Nonetheless, families—particularly of people with schizophrenia—are enormously on the line as caregivers. A recent study—going to be released in March by the Agency for Health Care Policy and Research, a five-year study of practices in schizophrenia and looking at actual care—will show that more than 70 percent of individuals in the study rely on their family, are in contact with their family, and in more half the cases live in the same place with their family. So, all I'm asserting is that ought to count for something, that those folks have demonstrated, and I think we've heard in various testimonies, a long-term, often difficult-to-maintain commitment and that it ought to be respected, and I was concerned, as I expressed, about what looked to me like a cumbersome legal authorization as though they had to demonstrate their bona fides once again. We need to understand what these disorders are like and we need to recognize in balance what that means.

PROFESSOR CAPRON: Could you offer language?

MS. FLYNN: Yes, I'll be glad to offer some language up. I wanted to just repeat again that a lot of the concerns that I have, and I continue to believe that we are going to make it if not prohibitive, almost impossible, to do research with certain subjects on whom we need research—*with* whom we need research because of the way we structured these recommendations. I could be made very much happier, and I think we would all perhaps find a way through this, if we could reexamine the issue of categories of risk. To have only minimal risk and every other kind of risk, and then to assign fairly simple procedures to that, creates enormous problems in neuroscience research. And so I think we could get out of that box by rethinking that issue. I'm not sure if there was another third thing. I thought there was a third thing you raised with me, but those are the two I remember.

DR. SHAPIRO: Okay, Larry....

DR. MIIKE: Yeah. Just on the last point that Alex raised about the State statutes. What I'm reading is this, that States should legislate a definition of legally authorized representatives in research. That's what I'm objecting to. If you're saying that States which have not defined what a legally authorized representative is or any kind of competency matters should do so, I don't have any problems with that. But the way I read this was that there was a recommendation that there be, specifically in the research area, and all I'm saying is that when you look at 50 States, they are not going to be that many that are going to be interested in this as a very big issue for the legislation.

PROFESSOR CAPRON: This is not a challenge to that, I just think we need to look at the statutes and see which of them are restrictive and would not include a decision about a person in research.

DR. MIIKE: If that's the case, then that's fine. But all I was responding to was this specific recommendation.

DR. SHAPIRO: No, I think that's a point well taken and Alex has made some helpful comments. We do need to clarify and rewrite that in some way that meets some of the concerns that people have. I think that's pretty clear, and so we'll attempt to do that. Laurie, do you have anything else right now?

MS. FLYNN: No.

DR. SHAPIRO: Thank you, Trish.

MS. BACKLAR: Alta brought up the fact that we seem to have dropped research advance directives out of the document, and in fact I think we have and that we were starting to call it, as somebody else noted, anticipatory planning. It isn't that I disagree with you, Laurie, about the importance of families being involved, because you certainly know that I feel very strongly about this, but there are many people, for instance, who do have these disorders, who do become estranged from their family because of the disease, and if one had some mechanism of anticipatory planning for people who have fluctuating decision making capacity or prospective decision making capacity like dementia or in their early stage of Alzheimer's—if they didn't have family members that they felt they could call upon, if you had some mechanism for the procedure, the process of that anticipatory planning, people could appoint a friend, somebody that they trust. And, that's why I don't want to see the whole anticipatory planning mechanism be dropped out of this.

MS. FLYNN: Can I ask a question? Because I may be the only one—in general, I would agree with what Trish said. I think any time we can create mechanisms that enable individuals who may have cognitive impairments to exercise control, to state their wishes, and to thereby help to direct their future, that that's an important thing and we should do it. What I think I've been hearing and what I think I've been reading is that while we may do that, we are bound almost to do it in a very generalized way that will not hold up, in fact, in the test of the specific study down the road, that we may not be able to see that through to actual implementation, and that's the only concern that I've heard that is at all persuasive to me, that we may set people up to think we've gotten them this thing, but down the road, depending upon the study, it may or may not in fact be true that that wish could be carried through. And, if there's a way to handle that—.

PROFESSOR CAPRON: You've been hearing that from researchers. Or do you mean like you've been hearing it here?

MS. FLYNN: I've been hearing that here as well as other things that I've read and as well as from researchers, that in fact if there were any challenge, if there were any question, or if there was just a heightened awareness of all of these issues that we and others are bringing, that that would not be seen as in fact strong enough and that it is therefore not very widely viewed as an actual implementable tool.

MS. BACKLAR: I want to go back to—oh, I'm sorry, I'm not allowed to.

DR. SHAPIRO: Go ahead, Trish, take most of the day—you've got some extra credits.

MS. BACKLAR: I think that we need to be very careful not to muddle this up with, and I've said this before, advance directives for end-of-life care. This is something that is quite different, and that's why I think Jonathan and I drew back from our earlier language because people were confused by the terminology. It doesn't mean that we have to throw the baby out with the bath water. I think that these kinds of mechanisms will work if we tie it to the informed consent process. And, of course we cannot be assured that anything that we recommend will be followed anyway. But that doesn't mean that we shouldn't make our best attempts to recommend things that might both advantage the subject and the researcher and advantage the trust that the community will have in the research process.

DR. SHAPIRO: The other—on this big issue—the other issue that came up in our last discussion was assertions and/or forecasts, but how many people would take advantage of such instruments given the asserting empirical evidence, which may be right—I just haven't reviewed it—that even though people overwhelmingly they would like to have something that deals with issues regarding around the end of life, they don't actually execute the documents. That may be true, but I don't know. But that was asserted, and the claim was that that was another aspect of this, which might—.

PROFESSOR CAPRON: Apples and oranges.

DR. SHAPIRO: Yes, well—and that came up, too. But I just wanted to reflect back, because that was an issue that came up. Okay, Steve. No? Alta?

PROFESSOR CHARO: I'd like to address the question of minor increment over minimal risk, because it's come up several times. I think it's possible that for the purpose of a draft going out for public comment, we may choose to write this up as something that's an option and ask for reactions. It may be that if there's no agreement among members of the commission that the appropriate thing to do is to lay out the options. My instinct, again seemingly constantly at odds with Laurie, is not to go down this road for the following reason: The IRBs currently are having a

tremendous amount of difficulty just dealing with minimal risk versus all other. And, there's new guidance that's being developed for them at this time. I fear that creating a new category called "minor increment" that applies only to a subset of protocols that most IRBs will see only on occasion because it's not going to be a generic category being added to all research just for this population. It's going to mean that we're creating a category that will be difficult to interpret—subject to misinterpretation based on whether people are hoping to do the experiment or not. My experience is IRBs usually are hoping to be able to approve the research. And that they won't have enough experience to check themselves. And, this might be an opening for abuse of a real sort. Finally, it's very difficult to write generic language here. Now, the fact that there is the option of the Secretary's waiver means that one can turn to that mechanism for individualized and very specific consideration of, for example, a proposal that says, "I have a subpopulation of people who are psychotic that can never give consent and I want to do a PET scan, which is not minimal risk and so by definition nobody could ever do this research unless you give me this waiver and now people can evaluate, the Secretary can evaluate, and people can comment on the very specifics of that particular risk and that particular benefit. And, the only question I have about the workability of that suggestion, which otherwise provides exactly the escape hatch we need, is how frequently that waiver has been sought and granted, and I think I remember we got that information once but I don't remember what the answer was.

DR. SHAPIRO: Once.

PROFESSOR CHARO: Once. Is it possible that that might be used more frequently and successfully, or is there some institutional problem in its use?

DR. SHAPIRO: I don't know the answer to that but when I read that particular proposal, it struck me that anything that requires the Secretary to approve something is going to happen very seldom.

PROFESSOR CHARO: Is it, in fact, the Secretary who approves it, or is it in fact OPRR with a bunch of signatures that come automatically after that?

DR. SHAPIRO: I don't know.

MS. FLYNN: May I ask an informational question?

DR. SHAPIRO: Yes. Laurie....

MS. FLYNN: Because I'm interested in what I think I heard you saying. Is it correct that we are moving to an understanding of the categories in research that IRBs will have only these categories?

DR. SHAPIRO: IRBs only now have "minimal risk" and "non-minimal risk." That's all they currently have.

MS. FLYNN: But there has been in fact in practice the use of this subset of "minor increment over minimal risk." I mean, it's been out there. I'm not sure why, but it's been out there and must have been seen as useful. Maybe someone can enlighten us as to why it was there if it's not an officially authorized category and why it's not going to be there any longer if what you're saying is that it's no longer going to be a way in which we can accommodate what are clearly gradations. There's a big difference between what we've seen as examples of minor, or minimal, risk and everything else. I mean, the next is such a huge and undifferentiated step.

DR. SHAPIRO: Okay, Jim.

DR. CHILDRESS: I'd be glad to yield to someone else. I think Alex wanted to respond to that...to clarify that issue and then I'd like to get a point in.

PROFESSOR CAPRON: Alta, I think it would be useful to have an alternative language here. Because as I understand it, Laurie's objection—if you look on page 143 under 7, there are the examples of minimal risk and greater than minimal risk, and your objection, which I credit, is that some of these things that are called greater than minimal risk are, in your view, in this minor increment.

MS. FLYNN: Right.

PROFESSOR CAPRON: And, so substantively, one way of dealing with this would be to have those spelled out as being in this intermediate class and I would like to know then how they get treated. In other words, do they get treated just like the minimal risk or just like the more than minimal risk...or is there somehow a third path, and to have

that available for comment, available for us all to look at, and then have it be part of what goes out in the staff draft for public commentary to us. I think it would be very helpful because you make very strong points about why it would be hard on researchers to have something like a PET scan be only allowed with the requirements that we now have for the greater-than-minimal risk. I'd like to know what's in the category and what are the procedures that would apply.

MS. FLYNN: Okay.

DR. SHAPIRO: Jim.

DR. CHILDRESS: That actually is the direction I was going, to, Alex, but a couple of other points on it. It doesn't mean that the points have been raised really—and I agree with Alta that we ought to get a public comment on it. And I'd like, Alex, I want to know what kinds of procedures and standards then of evaluation will occur for that intermediate step. But I want to know something else, too, from both Laurie and Larry—if we are able to carve out a category of "slightly more than minimal risk" and can work out some acceptable procedures and standards for dealing with that, would you then have any objection to what we do with the box? On 150, the last box, which would be then for greater than--substantially greater than—greater than minimal risk, whatever—and not potentially beneficial; that is to say, would that?

MS. FLYNN: That would take care of my problem.

DR. CHILDRESS: So if we can just carve out this intermediate category from your standpoint, though, it'd be okay.

DR. MIIKE: If I understand the question, I don't think we should have a blanket prohibition. I think we should have lots of hurdles to overcome before you can do something, but to have a blanket prohibition—.

PROFESSOR CAPRON: We don't have any.

DR. MIIKE: Yes we do, right now. Right now we have a blanket prohibition.

DR. CASSELL: Greater than minimal risk.

PROFESSOR CAPRON: No, it's not! You do it if you have the following things.

DR. MIIKE: Yes, but if you don't have informed consent you don't get anywhere.

PROFESSOR CAPRON: It's not a blanket prohibition; it says use people from whom you can get—.

DR. CHILDRESS: My question, then, is you wouldn't accept that, then, as a category even if we've already pulled out "slightly more than minimal risk, non-beneficial research" ... and develop procedures for that, and then you wouldn't be satisfied with this as the category for the maximal risk, the—.

DR. MIIKE: I'll write you my suggested option, but let's not forget the benefit side. There's no discussion about what we mean by beneficial research except for that section that talks about direct and indirect benefits. It does not say in the policy side what we mean and what qualifies. We need that. Because there's such a—I mean, all the focus has been on the risk side but we need the benefit side. Otherwise, many things are going to slip in on the benefits side to avoid having to meet the requirements on the risk side.

DR. CHILDRESS: That's true.

MS. KRAMER: I just want to go back to the matter of advance directives. I think as a practical matter that it would be shame to drop that terminology, because given the fact that people don't like to plan, why introduce another concept? At least you've got that one concept out there that people in the medical field are fighting for, so combine your efforts with it. I think that the plan, that the words, ought to be reintroduced.

DR. SHAPIRO: Eric.

DR. MESLIN: Not to interrupt the flow, but at previous meetings Commissioners expressed an interest to staff to start to work up an analysis of some of these categories of risk following from materials which we received from the FDA and others, and we were intending to distribute this analysis, complete with some very nice graphics, but there are a couple of glitches in it and we didn't want to distribute something that wasn't entirely accurate. It's 95 percent done, and it describes both what HHS requires with respect to the children's regs and distinguishes between the four

categories of not greater than minimal risk, more than minimal risk with the prospect of direct benefit, more than minimal risk with no prospect of direct benefit—all of which are incremental categories—and then the Secretary's waiver category, which is a fourth. And we've also looked at the FDA's protections in device studies and done the same kind of analysis given that that's material we received from them at the last meeting, which included their interesting categories of nonsignificant and significant risk. And, I don't want to confuse you with that terminology, but there are some existing Federal regulations that address these categories in a variety of ways, and although there was a movement two meetings ago to lump rather than split our categories of risk, staff would be more than delighted to provide you with this updated analysis so that you might be able then—sort of Alta's suggestion—to compare two different categories or two different frameworks, if you will. I won't attempt to prejudge for you whether it makes sense to harmonize our recommendations with existing regs for children or FDA regs for devices, but you do have those options available to you, and, as I say, staff would be more than delighted to circulate that material within 48 hours of you leaving this meeting. I'm trying to at least allow you the luxury of knowing that some of us have given this some thought and you might not have to deliberate more.

DR. MIIKE: Can I ask Jim a question to clarify? Jim, I guess I did not quite ask that question. I can live with an exclusion as long as there is something that you can appeal on a specific project basis like the Secretary's, so I guess it's a matter of semantics to me—what I'm concerned about is that there's a process—an in-depth process—there's a total exclusion without an appeal on a particular case. So, if we're talking about an appeal on a particular—I can live with that.

DR. SHAPIRO: Jim.

DR. CHILDRESS: Basically, if we would just glance for a moment to make sure I know where you are, Larry, in your thinking. If we were to look at 150 and if we, at the bottom of the page, were now to insert a box, another box, that would say slightly more than minimal risk, a nonpotentially beneficial research, and work out the appropriate kinds of procedures for that, we would still be left with this possibly large category of something that goes beyond that in terms of risk and nonpotentially beneficial research, and I guess what I'm asking you is whether for that leftover category you'd be willing to accept the kinds of requirements that are listed here. Or would that go too far—and of course we can talk about the exceptional—.

DR. MIIKE: Again, as I say, if there is something like an appeal to the Secretary—.

DR. CHILDRESS: Then you would, okay. Thanks.

DR. SHAPIRO: Okay, Alta, you're next. Then Trish, then Rhetaugh.

PROFESSOR CHARO: Do I have a hand up? I give my turn away.

DR. SHAPIRO: Trish.

MS. BACKLAR: Have we agreed that minimal risk is that experienced by the population being studied in their everyday life that—have we agreed on what we mean by minimal risk?

DR. SHAPIRO: Alta.

PROFESSOR CHARO: Jonathan's been asking on E-mail over and over for people to respond to this and I'd just like to share...

MS. BACKLAR: And I did respond.

PROFESSOR CHARO: ...and I'd like to share for the record what I told him privately, which is that after having ducked several times, my vote for the moment is that the definition of minimal risk should stay the same for everybody, which is the daily risks experienced by the general population. Again, for very pragmatic reasons, IRBs already are dealing with many subjective factors and I would love to keep the number of hairsplitting moments to a minimum there—there are plenty of them already—and so a consistent definition across all populations seems better than special definitions for special populations.

MS. BACKLAR: Does that mean that minimal risk means those risks experienced by healthy people in their everyday life—is that what you mean?

PROFESSOR CHARO: Yes.

MS. BACKLAR: So, then, for a population like people with schizophrenia, their risk is so much higher, so how are you going to measure minimal risk? Their minimal risk is very, very different...

PROFESSOR CHARO: No. When an IRB gets a protocol and has to deal with it, it could qualify for minimal risk treatment but that doesn't tell you what their final judgment's going to be about the acceptability of the protocol. A procedure like a blood draw is presumably minimal risk, but they always exercise judgment and say, "But you know, in this particular protocol you're dealing with people who might get very excited and upset at being stuck with a needle so we think there's still a problem with this protocol even though a blood draw is usually treated as minimal risk." I mean, IRBs do exercise that judgment. The minimal risk determination is only about the procedures the IRB is now required or not required to follow in terms of who has to be there in subcommittees and things like that.

DR. SHAPIRO: Let me make a suggestion on this set of issues dealing with definition of risk and how many categories of risk that we're going to deal with. As Eric indicated, the staff has prepared some analysis of this. Let's get that finished and out so we can discuss it. It's a very important issue, just how we define it, so I don't want—it's extremely important, and I think, in fact, what decisions we make there could interrelate with other aspects of the analysis and not exactly—may not be an independent thing. So, I think we should carry on further discussion of that once we receive some initial suggestions from our staff on this issue. I take it from the Commissioners' conversation that there is some concern about whether we have enough categories—that is, whether we should have minimal risk, minor increase over minimal risk, and something more than that, and then how we define those categories. So, let's take a look at what work we can put together on that and make at least some initial recommendations on this and then we can have I think a somewhat more informed discussion. Yes, Rhetaugh . . .

DR. DUMAS: I am satisfied with the categories that we have. I'd be happy to see the information that comes out, but I feel very strongly that if the procedure is going to have risks by the subject and there's no way to obtain consent, then it should only be done if there's a legally authorized person who can make decisions on the behalf of that other person. I think that whatever we come out with should improve the situation and we know that there are certain populations of people who have been exploited and we have case examples, and I think that we have to be very careful how we formulate our recommendations such that we can make some improvements rather than perpetuating a situation that we're trying to amend. And I think that when you get into splitting hairs about whether it's slightly more than minimal, it just encourages people to push forward, and I don't want to feel that anybody is going to be forced to participate in a research project that's not going to benefit them at all and they can't consent.

DR. SHAPIRO: I propose to the Commission that we could take two points of view: Here's what it would look like if you only had two categories of risk; here's what it would like if you had three categories of risk. No matter how many categories you have, you're going to have tough cases. We're not going to be able to define all those tough cases, and all of a sudden, the IRBs are going to have to struggle with those regardless of the number of categories we have. And as far as getting science done, there are two ways to—at *least* two ways—to does it. One could change the definition of minimal risk to a category where you'd be uncomfortable having any other category beyond lots of risk. Or, you could—and, you know, whether you put that bar up or down changes it a lot whether you want to have a third category. So, let's try to think this through systematically if we can and provide some suggestions—some alternative suggestions that we can discuss. Eric?

DR. CASSELL: At the moment I haven't heard a way to go by it, and I'm hoping that what Eric distributes to us will at least give us an idea that—if we can only get by this problem, and of course one of the ways is we give the IRBs more latitude but we're nervous about doing that, so I just want to come up with some useful suggestions in this regard.

PROFESSOR CAPRON: Can we have a discussion on this question of what disorders—?

DR. SHAPIRO: Yes, that's where I want to go next. I really wanted to get back to Alex's issue, which is a substantive focusing on the title of our document. Now, that title's gone through a number of evolutions over time as we've tried not to make sure that we weren't stigmatizing people, treating people in some inappropriate way or—and therefore we came up eventually with this particular title and Eric began this meeting, or began part of this meeting, by suggesting that this includes just about everybody who's sick. I think it's more or less what you said. And, that's certainly not the intention of this report. We're not trying to rewrite all of the regs and guidelines here; we're trying to deal with regs and guidelines for a population which I think we all have a clear idea who they are and now the question

is Alex's question: What's the domain? I took the domain to use another word which perhaps is got its own problems. It'd be people with mental disorders of one kind or another, and not include people who have very serious diseases of other kinds and therefore are upset and their minds are not as acute as they might be. I was not thinking of those people. That was my interpretation.

DR. CASSELL: But you were thinking of people who are very sick with their mental disorders.

DR. SHAPIRO: Yes, of course.

DR. CASSELL: And there's no difference in some ways between them and people who are physically—.

DR. SHAPIRO: I understand that, but we really need to decide whether the domain—I had assumed people with mental disorders of one type or another—is really what we're talking about here. Yes?

DR. BRITO: Yes, I raised this issue a little bit earlier about that in the context of the first recommendation...and I think the title is fine, but I think somewhere in the body of the paper we do have to define that. But, even if you just limit it to people with defined mental disorders, I think there's a problem there, too. For instance, this morning the public comment was brought up, even though it was a child study, still children that are aggressive—well, all the public testimony we've heard is about, for the most part, schizophrenia and manic depressives, etc., but what do you do if you have an adult population that is impulsive? That's considered a mental disorder. ADHD in adults is considered a mental disorder. Are we talking about them, too? Do they have the capacity to make a decision in some situations? Probably not. In some situations? Yes. Or, most situations, yes. So the point is that that's where it's confusing to me when we say "this population." So, somewhere in the context we have to talk about that we're just saying—and that's where I was asking Laurie and the rest of the people—the rest of the Commission, all right when we're saying "this population," without stigmatizing anyone are we going to limit it to schizophrenic individuals, manic depressives—where does it start and where does it end? Because even, you know, we've heard today that 50 percent of schizophrenics can make their own decisions. That might be more than in other mental health disorder we haven't even talked about. So, that's where my concern is in here.

MS. BACKLAR: On page 10 we have a list that Paul Appelbaum put together for us. Very clearly set out the nature of disorders that affect decision making capacity. When I spoke about 50 percent of people with schizophrenia being able, that was in a particular study that I was alluding to that Paul Appelbaum was doing in terms of other people. I don't want people to walk out of this room and think that I just made a blanket statement.

DR. BRITO: Nobody's going to think that. That's not the point of that.

MS. BACKLAR: Okay. But on page 10 Paul talks about dementia, delirium, depression, schizophrenia, other disorders.

DR. BRITO: Okay, Trish, that's my question. Are we limiting this population to mean the mental health disorders described in this introductory chapter—this first chapter? Are we saying this paper talking about disorders affecting decision making capacity is going to be just these disorders and this is where the extra provisions are going to be required?

MS. BACKLAR: As I understood it, we are trying to fill a gap that is in 45 CFR, and that gap was left because it was a document put together in the late 1970s by the national commission called something like Institutionally Mentally Infirm—I can't remember—Recommendations. And that looked at a group of people who I believe are described by Paul Appelbaum in our introductory chapter, and that's what we want to do. Our intention is to fill that gap. Am I wrong?

PROFESSOR CAPRON: Well, you're only wrong to the extent that that group was a little easier to define because those were institutionalized as mentally infirm—and even there, of course, that report never was able to gather enough consensus in the relevant competing communities to be translated into regulations, which is why we had this lacuna in the present regulation. So, it's one thing, it seems to me, to say that we know we're talking about mental disorders here, but if someone challenges you and says, "Well, *why* are you talking about mental disorders that affect decision making capacity if"—suppose Eric Cassell's research were not something that was orally reported here but had been replicated and peer-reviewed and it was now widely believed that all medical patients with serious illnesses have disorders affecting their decision making capacity, and indeed it was very hard to distinguish between the effects of those

disorders on many decisions that they made and these mental patients. Would it be that we would still want to have a separate set of rules, and we would want to, in fact, put the word "mental disorders" into our--which is not now here—but put it in because we think that this is a more vulnerable group, this is a group whose mental condition, whose disorder is of a chronic nature—either it's progressive or it's fluctuating—I mean, is there some reason for treating them differently than patients who have cancer and who will be enrolled in cancer research despite the fact that Eric's study would show that they have problems with their judgment for which some supplemental process or something else is going to be necessary before we can have reasonable confidence that they're making the judgments that Eric would regard as authentic or something, or autonomous.

DR. SHAPIRO: I have an answer to that, but I'll let Tom and then Trish—.

DR. MURRAY: Life is full of continua and you can't solve all problems at once. With those two principles, let me just speculate a little bit. Suppose—.

DR. CASSELL: We'll solve this 'cause it's not tissue. [GROUP LAUGHTER]

DR. MURRAY: Right. I wish I could make your life harder. It looks like you're doing it for me. No, actually, I think I'd like to try to make it easier. Let's suppose that the study was of cancer patients, but what we were particularly interested in was, because your hypothesis was that at least a certain population of advanced cancer patients were suffering very severe cognitive disorders, disorientation. That was your assumption going in. Would you want those subjects—"subjects" covered by this rule? And I think the answer is yes, you probably do. And so you might end up with a description that looks something like this. The words are by no means ideal, but, if you're investigating persons with a disorder, whatever the mantra is, or persons who might be regarded as having—that's not good at all, but basically people with a diagnosis of one of the listed cognitive disorders, disorders affecting cognitive function, or people whom you have reason to believe might have disorders in their cognitive function, even if they don't meet this diagnosis. Now, you don't want to have every patient listed in an oncology trial to be included in that category, I think—do you?

DR. CASSELL: No. But there are some of them who are cognitively impaired and then they should be protected.

DR. MURRAY: Yes, and there should be ways of solving that problem, too, particularly if—.

DR. CASSELL: There are.

DR. SHAPIRO: Trish?

MS. BACKLAR: Well, very early on in our discussions I remember trying to put these into various categories so there was prospective incapacity and fluctuating incapacity and so on and so forth. Oddly enough, it seems to me that our recommendations may be useful beyond what was our intended filling of a gap, and I don't think that's all bad. We never talked about these wraparound studies at the end of the paper and I'm concerned about that. I was planning to discuss it with you afterwards, but I don't think it's fair because maybe we should discuss it now. I'm worried about the therapeutic misconception; I'm worried about the way they're not thought out very well; and I think that we need to have some discussion if not today another time. I have a whole long list of other things, but that seems rather important.

DR. SHAPIRO: My own, at least initial, response to this issue I think is similar to what Trish just said, and namely that this is a set of recommendations designed for a particular population. We have to think of the right way to describe them. They may very well have application elsewhere. But our attempt here is to fill a gap, and maybe the next step, if that seems reasonable, is to look at the broader issue for people with other kinds of disease which also affect the cognitive fascia. I think there are, as you were suggesting, Alex, in your remarks, some additional reasons than just filling a gap, which I think distinguishes some of these cases—I wouldn't say in every case, but it's the recurring nature of chronic—it's not the only chronic disease, of course—but I think there are, if we thought about them, some distinguishing characteristics, which helps a little bit.

PROFESSOR CAPRON: But that's not what our report says now, because our report now, in talking about delirium, for example, cites studies in the intensive care unit and says the patients in the intensive care unit may have a temporary but severe impairment of the decision making capacity. So suppose that the agencies involved in the common rule were to take our report and say put it out for comment, and then when the comment was done decide that the language we had suggested should become part of a special subpart describing this, and they just used that language.

Now, someone would say, well what did they mean? They would go back to our report, and in our report a conscientious IRB would find this discussion of delirium, which arises in intensive care unit patients. In that case they would say, "Now when you come in to study surgery or various other forms of treatment for patients in the intensive care unit, you need to have this process." Now, if we don't mean that, then having discussed that we're going to say, "Although there are common similarities, we are now going to limit ourselves to those conditions usually thought of as mental disorders because of certain characteristics of the patients in this population—marginalization—you know, difficulties relating to their community and their families, often institutionalization, etc., etc., etc., and so we're going to treat them differently," although, as Tom says, there's a range and you don't attack everything at once. But we should be clear because...

DR. SHAPIRO: I agree with you, exactly with what you said. As a matter of fact, one of the more modest concerns I have of the draft as a whole is I would like, as we go ahead, to substitute more of our examples from the restricted population, so to speak, than from the broader population, because I think all the examples are pertinent, at least not that, but I think that some of them, a number of them, just don't come from the population we originally started out to think about. And, so, I would like to sort of enrich us. In part we'll do that through these protocols that we'll look at and bring those examples in. But, I agree with you that we have to change some of the language in here and the structure to accommodate that.

PROFESSOR CAPRON: I mean, our protocol search is not looking in intensive care units.

DR. SHAPIRO: No.

PROFESSOR CAPRON: It's only looking at mental disorders.

DR. SHAPIRO: That's right. Exactly. But it will give us examples, exactly, that'll substitute one for the other. Other comments or questions? I recognize it's the end of a long day, but comments are helpful.

PROFESSOR CHARO: Just a correction for the record, because I misspoke before on the definition of minimal risk. And the question was, "With reference to whom?" and I said, "The general population." Somebody said, "You mean healthy people," and I said, "Yes." The answer should be "No." The general population, which is healthy people and sick people, so that's a slightly lower threshold. Okay? That's all.

DR. SHAPIRO: Thank you. Jim....

DR. CHILDRESS: If you're moving, Mr. Chair, toward adjournment...

DR. SHAPIRO: Yes.

DR. CHILDRESS: ...maybe one question we could think about is whether we think with the incorporation of the kinds of changes that have been proposed here, including in some cases, presenting alternatives that go this way and go this way, and with Jonathan, Eric, myself, and anyone else who would like to volunteer or would be willing—not necessarily willing, but—to join us to put something in shape over the next two or three weeks to deal with these issues, then whether you'd think we're at a point where it'd be good to get public comment. I think that—I have a couple of reasons for thinking it might be good to go that direction. I mentioned that at the very outset of our discussion this afternoon. One is, there is the time consideration. We're not meeting again until May and then after that until July and so forth, and it'd be good to get some input, I think, well before then. Second, I think that it will be easier for us to sustain our personal and vigorous investment involvement in this process if we get some outside input, and—because we've spent a lot of time going over particular parts and I think it would be helpful, so I guess my proposal would be, if it's all right, Mr. Chair, that we consider going that direction and going ahead and getting public comment sooner rather than later, but stating very carefully that this is a draft report and we're going to use language now that Harold has suggested and draft a report for the Commission rather than of the Commission and thus we're not signing off on it any way. We're getting input on some matters that we're continuing to reflect on and will continue to work on.

PROFESSOR CAPRON: And if you do that at a time when it's a draft which hasn't yet been before us and it's being circulated publicly prior to our next meeting for comment, then it is in truth something that no one could say is the Commission draft because we won't have seen it in the point that it's put out for comment.

DR. SHAPIRO: Some of us are still members of the public or something. But, in any case. I very much favor getting it out for comment. There are a lot of people out there who I think, once they see it and know a document is available, will in fact go arrest their attention and we'll get valuable feedback, and I can't see any downside to it, as a

matter of fact.

DR. CHILDRESS: And my hope would be, if I might add to it, that if we're able to do that in a timely fashion, allow a month, say, for feedback, there might, as information as responses are coming in, we might have to staff begin to analyze those and, say, if we have a cutoff date of—of, say, April the 20th or whatever, that we then put those in final shape and kind of an analysis of the major types of objections that are occurring and so forth and try to sort some of those out, and then at the May meeting talk about how, given what we're hearing from people who are responding, we might want to revise the draft that will have been circulated. That's the kind of direction I would have proposed.

NEXT STEPS AND ADJOURNMENT - Dr. Harold T. Shapiro

DR. SHAPIRO: That sounds quite fine. I hope there's nobody that has any objection. So, first of all, let me in closing thank all Commissioners for a lot of very useful conversation that we've had in the last day and a half and to—we're now on a new schedule, so to speak—we're meeting every two months. I will, for purposes of assisting our colleagues on the West Coast—we will try to schedule the meetings where possible where we go a day then half a day as opposed to the reverse—half a day, then a day. But we'll just have to see—we're going to try to schedule it that way as much as we can. So thank everyone. I want to thank the staff for their assistance and help, and we look forward to hearing from you all. I said before that we would be making some assignments regarding the tissue report for two or three people who worked rather intensively on that. We will do the same in this support. I've not yet talked to Jim about it, but we will do the same. I think that's necessary to get this into shape. So, thank you all very much.

ADJOURNMENT, 4:59 p.m.