# 42nd MEETING

# NATIONAL BIOETHICS ADVISORY COMMISSION

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

# I N D E X

# I N D E X (continued)

## Hawaii at Manoa

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

**DR. SHAPIRO: Colleagues, let's begin. I apologize first of all to Mr. Tozzi, who we will hear from in just a moment. I recognize we are 20 minutes behind time and you arrived on time so 157157I apologize to you for keeping you waiting.**

**We just ran later than anticipated this morning and probably the lines at the lunch counter were longer than anticipated. So it is a combination of those things that we are starting late.**

**But Mr. Tozzi, who is from the Center for Regulatory Effectiveness, has asked to speak to us today. Our rules are five minutes. If you exceed five minutes I will remind you and ask you to bring your remarks to a close after that if that is necessary but we look forward to hearing what you have to say.**

## PUBLIC COMMENTS

### JIM TOZZI

**MR. TOZZI: Thank you, Mr. Chairman and distinguished members of the Commission.**

**Rest assured, I am on a number of advisory boards and if they all started only 20 minutes late made up of academics I would find that to be a big accomplishment.**

**As you stated, I am with the Center for Regulatory Effectiveness, and I will just give you a minute on what we do.**

**We are an organization that reviews and studies the federal regulatory process and so we look at a range of scientific and policy issues that are udder concern in the government and see how they impact the regulatory process and if we think there are ways to improve it we make recommendations in a variety of ways.**

**I am speaking on behalf of our board of advisors. The board of advisors are limited to ex-career heads of regulatory review in the White House Office of Management and Budget.**

**I think it is always good to tell a little bit about the funding of the center. We do not have any members. We get contributions threefold. We get donations. We get work product and we get services from trade associations and private firms. The groups that participate at any point in time in the center -- there is a whole gamut of the -- from software manufacturers to internet providers, financial services, industry, oil, chemical, telecommunications, almost the entire gamut.**

**So I would also invite members of the commission to visit our website. It is "thecre.com." It is a site sort of nerdish in content but it is**

**used very heavily by federal regulators and the regulated industry, and we probably have as many hits from overseas as we do here. The site is cached around the world. It is in universities and it is updated quite a bit.**

**So I appreciate this and I would like to make a recommendation to the commission. However, on the commissions I have been on, one of the common -- first things asked is, is it within our charter. And I think the recommendation I am going to make to you most certainly is in your charter.**

**As you are aware, it says the National Bioethics Advisory Board will provide advice and make recommendations to the National Science Technology Council, other appropriate entities and the public, and the recommendation I am going to make to you today is to make one to "one of those appropriate entities."**

**It goes on to say the commission may accept suggestions for issues for consideration from both the Congress and the public and we would meet dimension.**

**And, finally, your charter vests the institution with the statement that the commission may specifically identify the federal department, agency or other entity to which particular recommendations are directed and request a response**

**from the federal department, agency or other entity within 180 days.**

**So I think I have -- I am addressing most certainly the right group with the right institutional clout and most certainly the programmatic and knowledge.**

**What is my request? My request is very simple. I think the commission ought to review the recent decision by the Environmental Protection Agency not to use or not to abide by the Common Rule and to discourage the use of human data in the federal regulatory process.**

**I am not here in any manner to suggest what way the commission may come out. I will give you a couple of my concerns but obviously this is within your charter and I think it is of particularly importance given what I see as the second item on your agenda today.**

**Now as you probably know better than I that the Common Rule applies to research done by federal agencies with federal funds and that the Common Rule for 17 agencies historically and for some period of time has allowed the use of human test data.**

**Virtually all the scientists that I spoke to in a number of agencies says that they use it and it applies to research -- human research done with nonfederal funds by private entities. There is a**

**legal question of whether it is automatic or authoritative but I do not think this is the body to discuss that particular issue.**

**Nonetheless, EPA's position, not necessarily yet of their advisory boards, is not to use human test data in the development of tolerances and regulatory requirements for pesticides. This is at variance with the historical practice of the agency.**

**It is at variance with a number of other federal regulatory agencies and it most certainly raises questions as if the federal government has federally appropriated funds to perform research. And if a nonfederal entity were going to do it subject to the Helsinki Convention and the appropriate institutional review boards, why that would be prohibited.**

**I think this is of extreme importance because of the nature of the work you are doing on your second item and I think that this issue that EPA has taken if adopted by the other federal agencies probably would make your second paper not very relevant if it were adopted as a government-wide policy.**

**I have been around the regulatory business 20 years in government and 20 years out of government, and macro regulatory processes start with one federal agency going unchecked. So I really**

**think this is of importance for this group to look at.**

**I think the database on EPA's use of test data is clear. They use it now for MTBs, SO2, N02, C0, particulates, and a number of other things. And so this policy that is coming which we think at the center has government-wide implications. It has international implications, in fact we -- a lot of our members are multinational companies outside of this country are very concerned.**

**So, in summary, my recommendation request to the panel is several-fold. First, EPA is working on its -- this policy on human testing. The timing is good because you are working on the same issue from what I gather from your agenda item. And, third, we have a very substantial white paper that the center has written on it, it is available through our site, that lays out what we think the pros and cons are of this.**

**And so my request is to you both in terms of your charter, in terms of the work you have under way, that there is no group I think that could -- that is constituted better than to have a range of expertise to address this issue than this advisory committee, and our request from the center is that you address that at the appropriate time.**

**Thank you, Mr. Chairman.**

**DR. SHAPIRO: Thank you very much for your remarks. I do want to point out to commissioners there is a copy of this testimony, I think, or your materials that was in front of you as we came in today.**

**Are there any questions for Mr. Tozzi on this issue that he has raised?**

**Alex?**

**PROFESSOR CAPRON: I have to confess that I am -- having not had a chance to read through your full statement -- I am unclear whether the action of the EPA that is -- that you believe is problematic is -- it is one of three things. It is either the July statement which places some limitations on the use of nonfederally funded research data or it is the statement in the staff background paper which seems to take a narrower view that there will be no nonfederally funded data used, or it is the underlying decision about the way in which the agency's regulatory standards are -- or regulatory decisions are supported. That is to say the use of animal data when there is no human data.**

**And it -- I think we -- I want to know whether you would agree with me that to the extent that it is the latter that is the real complaint of your group with the way the EPA is going about things, that falls outside our jurisdiction. You**

would agree with that, is that right?

MR. TOZZI: Yes, sir. Let me address that. On the second -- I am very aware of the second or third issue that you raised. The use of animal or mechanistic data to upgrade in hazard designations is -- or classifications as a known carcinogen. No, I agree that would be out of your charter.

In fact, it is in a very good tribunal. It is called the District Court here. It is Tozzi versus the EPA. That is in litigation under the dachshund (sic) thing and the judges are hearing that case and we expect a decision pretty soon.

My concern is really the second one, sir, that you stated, that the first -- the July statement appeared to be written by an economist which my -- it says on the one hand you can do it and on the other hand you cannot.

But it is the second -- it is the second one, sir, that is the concern. The statements by the staff. The statements in meetings is that they have this interim policy and they are not going to allow -- and my understanding is they are not going to allow the use of human test data for the calculation of NOELs, nonobservable effect levels.

And the downside of that is -- and I -- we have not finished our studies but we looked at other people -- where they have used human test data, I am

advised, that a number -- maybe as high as 30 percent -- have resulted in more stringent regulation as a result of the human test data.

But in answer to your question it is the second and most certainly not the third, I agree.

DR. SHAPIRO: Could I just ask -- there is two July statements. I have not had a chance either to read carefully this testimony. I apologize. One is July 27th. On the first page you quote from it. That is the same statement that is on page two and comes from the same statement?

PROFESSOR CAPRON: No. The one on page two is, as I understand it, is the background paper which accompanied a meeting in November of 1999 of this joint scientific group.

MR. TOZZI: Right.

DR. SHAPIRO: I see. Thank you.

PROFESSOR CAPRON: And, again, let me see if I understand. Part of this would be a complaint about what is happening during an interim period and the other would be a complaint if there were to be a permanent situation in which no such test data could be accepted because that would influence your larger concern, which is the one that is in the District Court.

As I understand, this is a statement here that says they will not take the data from

**nonfederally supported studies until a policy is in place that can ensure they meet the highest scientific and ethical standards. Now is that taken to be a statement different than that they meet the requirements of the federal rules? Is that what your complaint is?**

**MR. TOZZI: No. If EPA's policy were to state -- I do not think I can speak for everyone in the center but I can speak for the board. Of course, if you have human testing you are going to have to have IRBs and people responsible for the conduct of those studies and it cannot be, you know, a laissez-faire type approach.**

**If that were the policy that would come out of this subject that the IRB constraints were do-able, we do not see that problem.**

**The problem that we see is they are going to prohibit the use of human testing in the calculation of these NOELs, period. And that most certainly is the -- as I understand the policy now -- in fact, there was some products, I think, that were discussed last week at EPA that they changed their uses on as a result of not using human test data.**

**So the answer to your question is, no, if what came out was, yes, you can use it just like you do on federally funded data with proper institutional controls and IRBs, I do not think there would be a**

**problem.**

**The problem is an outright ban for NOELs and let me -- let me tell you what I think some of their concerns are.**

**Their concern is that if you have a pharmaceutical going through Phase I of the FDA that "the pharmaceutical supposedly may generate benefits and, therefore, human testing down the line has some impacts." But I am involved in the licensing of drugs and in a Clinical I, you generally test to see if the stuff is safe before you really look at it. So you do not know what benefits are going to come out of Clinical I. In fact, a lot of things we go through never come out of the system so I am not sure I agree with that.**

**And the second statement is that on these pesticides and related activities there are human health considerations. One, there are a lot of Third World countries that are going to need these type of products.**

**And, second, not studies done by the center that are quoted, that many times the use of human data results in more stringent regulations than if you did not use the human data. But that is their concern. It is that window on the NOELs or margin of error or whatever -- or exposure that they would be using.**

**DR. SHAPIRO: Thank you.**

**Eric?**

**DR. MESLIN: I just think it is important for commissioners to know -- I have mentioned this in previous correspondence -- that I was a federal member of the SAB/SAP, the Scientific Advisory Board and Scientific Advisory Panel that met on the two occasions mentioned in Mr. Tozzi's testimony. That has been the subject of both media reports and other conversations.**

**I say that because there was a significant ethics presence on that SAB/SAP, including the former director of OPRR, Gary Ellis, Professor Sam Gorbitz from Syracuse University, Jeff Kahn from the University of Minnesota, and Art Kaplan from the University of Pennsylvania, and that process which took a considerable amount of time resulted in both some minority statements by the panel and caused, I think, a certain amount of revisiting of the EPA's policy.**

**So just to ensure that the context is correct, part of -- in response to Alex's question -- is that the -- my understanding of the EPA's decision is a decision to make clear what their policy is at this time right at this time. It may not be their policy for all time.**

**I am happy to make available to all the**

commissioners and others, if they need it, the background materials that this conjoint board utilized.

DR. SHAPIRO: Thank you. Other questions for Mr. Tozzi?

Well, thank you very much for coming today and we very much appreciate your remarks and your concern.

MR. TOZZI: Thank you for the time.

DR. SHAPIRO: I want to now move on. I am hoping to be able to enlarge the time we have tomorrow morning to return to the International Report. That means getting started on time, which is always difficult for us on the second day it appears. But the amount of time we have will be directly related.

We can move some of the other items. We can condense some of the other material so we can get probably at least an additional half hour from what is scheduled but I really would like to use what is scheduled. We have to revisit -- we have to visit Chapter 5 and we have to revisit a number of issues on Chapters 1 through 4 at least to the extent that time allows. So it is just an exhortation for us to begin as soon as we possibly can tomorrow morning.

Depending on where we are tomorrow we will have to decide as a commission what the next step in

our process are and how we will review materials and when we will send what out for public comments and under what conditions but that we will all deal with tomorrow morning.

Let's turn now to the agenda we have here before us this afternoon and let me turn to Marjorie for an overview of the work to date. That will be a relatively short presentation, as I understand it. There may be questions from commissioners. And then we will move directly into the series of panels we have here this afternoon.

Marjorie?

## ETHICAL AND POLICY ISSUES IN THE OVERSIGHT OF HUMAN SUBJECTS RESEARCH

## OVERVIEW OF WORK TO DATE

## MARJORIE SPEERS, Ph.D.

DR. SPEERS: Thank you.

This afternoon our panels will be focusing on the broad topic of providing protections and we will be looking at that from three different perspectives.

Our first panel will address community based research and will be looking at several of the issues involved in conducting research with communities. Basically what we hope to address during that discussion will be what happens when the community becomes a collaborator in the research process.

**Our second panel is comprised of individuals who have or who are participating in research and I will say more about those individuals when we introduce the panel.**

**And then we will end today with the paper that was commissioned by Dr. Kenneth Kipnis regarding vulnerable populations.**

**Tomorrow morning we will be offering for your view -- this is not a pay per view but just offering for your view a video that was recommended that we show to you regarding issues that individuals have about participating in research. The video is called "We all have our reasons," and it deals with community perceptions of HIV vaccine research. It was produced by the University of Pennsylvania, funded by the Centers for Disease Control and Prevention, and the National Institutes of Health.**

**The video won the National Educational Media Network Award of Excellence.**

**What we are proposing to do because of our busy schedule is that you join us here for breakfast, get coffee and a muffin at 7:30, and then we will show the video, and I think that that will help Harold then to start on time as he would like to do tomorrow at 8:00 o'clock.**

**Then we will move tomorrow into three other panels. One panel will be addressing practical**

**issues related to the assessment of risk and benefit. And then we have two panels that will be looking at perspectives of the oversight system. One perspective will be from those of IRB administrators and institutions and the other from the perspective of researchers.**

**I want to call to your attention Tabs 3B and 3C. If you have not had a chance to look at them you may want to by tomorrow's session. Tab 3B includes in it responses to letters that we sent to IRBs and to universities soliciting their comments on the federal oversight system.**

**Tab 3C presents a summary to date of the town meetings that we have conducted where IRB administrators, researchers and members have come to talk to us.**

**I think what you will find if you review those tabs is that there is a convergence of issues that we are hearing about and that I imagine you will be hearing about tomorrow.**

**Just to preview for you very quickly, in September we will be dealing with issues around privacy and confidentiality and conflict of interest, and then we will begin at the September meeting and finish at the October meeting looking at various -- what I am calling quality control mechanisms.**

**This will be looking at the assurance**

process, site visits, accreditation, certification, licensure and so on.

So at this point, I guess, what I would do is take any questions that you may have and then we will move into our first panel.

DR. SHAPIRO: Alex?

PROFESSOR CAPRON: I have a question about where we stand on the completion of the task of assessing what the agencies' rules are, how complete they are, what gaps, as well as anything about their implementation.

DR. SPEERS: Thank you. That is a -- thank you for the question. The -- Kathi Hanna is working on a report and has just recently given us a first draft of that report to review.

I would imagine that we will have that report complete and ready for you to look at by September and possibly sooner we will be able to send it around via e-mail.

DR. SHAPIRO: Any other questions?

Okay. Marjorie?

DR. SPEERS: Okay. At this time we would like to begin with our first panel on community based research and I would like to ask Dr. Vincent Francisco and Ed Trickett to join us at the table.

## PANEL I: COMMUNITY-BASED RESEARCH

DR. SPEERS: Great. Welcome. Thank you for

**joining us here today.**

**And just to give a little bit information, Dr. Francisco is the Associate Director of the Work Group on Health Promotion and Community Development at the University of Kansas.**

**Dr. Trickett is Professor of Psychology at the University of Maryland.**

**Both of them have asked to -- have been asked to provide a brief statement regarding community based research and then following their statements we will open it up for discussion with commissioners.**

**And it does not matter which one of you goes first. What we tend to do is whoever is listed first on the agenda generally goes first so I am going to ask Dr. Francisco to go first unless you feel differently.**

**VINCENT T. FRANCISCO, Ph.D,**
**ASSOCIATE DIRECTOR, WORK GROUP ON HEALTH PROMOTION AND COMMUNITY DEVELOPMENT**
**UNIVERSITY OF KANSAS**

**DR. FRANCISCO: Very good. Thank you very much for the opportunity to discuss some really important work with the commission today.**

**(Slide.)**

**I would like to frame my comments and the materials that I have provided with a little bit of**

**background about the kind of work that myself and my colleagues at the University of Kansas have done and some of the experience that we have had and use that as a grounding for the framing of some of the comments and some emerging issues that I think are worth consideration and addressing by this commission.**

**I have been involved with the IRB at the University of Kansas for about a little over eight years now and have had experience doing community-based research in places from Maine to Hawaii and most places in between as well as some emerging research that is occurring in other countries. As much them adopting materials and procedures that we have developed at the University of Kansas as the beginnings of relationships with folks in some of those countries.**

**(Slide.)**

**There is a variety of emerging -- what I would consider emerging issues that are beginning to present themselves over the past eight plus years based on some new relationships that are emerging as a result of changes in federal funding, as well as changes in local standards for control and involvement in research.**

**Most of the research that we do at the University of Kansas involves us being a full and**

**equal partner with community members, community organizations of a variety of different kinds, whether NGOs and community based organizations themselves or more informal partnerships such as coalitions and community collaboratives in a way that is somewhat different from most mainstream research is conducted within university contexts explicitly.**

**This kind of partnership is not necessarily discussed or provided for within the federal regulations prior to recent times but it is interacting and somehow struggling with these regulations and people who are implementing these regulations in university contexts.**

**As an example, we have got a collaboration going on between us and several communities in Kansas itself. We have had a very difficult time working within the context of the regulations allowing the folks in the community complete control over the implementation of the intervention, with us providing a certain amount of technical support for what I would consider core competencies such as leadership development and things like that, and then us coming to the table as folks who are experts in data collection systems, partnering with folks who have developed a community intervention that to a certain extent is a vast experiment, and overlaying a data collection system that would be fair and appropriate,**

**and is in keeping with local norms, and then getting that approved within a university IRB that also wants us to take full responsibility for the independent variable itself, which is the usual or the more normal form of research where universities are involved with folks within a community.**

**So it brings up several different issues. One is the possibility for a new definition of researcher, a new definition or expansion of the definition of what is research, consideration of standards for informed consent, as well as a few other issues that have come up in the context.**

**(Slide.)**

**So the possibility for a new definition of researcher emerging. There is a new relationship, which I just began to describe, between traditional researchers and participants in research.**

**This new relationship is really due to changes in community based grant making by foundations, state and federal agencies. These new researchers really are community members. They are folks who develop interventions for changing behavior among large numbers of people at a local level a very small degree for a variety of community problems and who hire others such as university researchers and a variety of consultants out there to create data collection systems and provide some information to**

**them about making -- helping to make decisions at a local level.**

**(Slide.)**

**There is a possibility, I think, in this context for a different definition of research and I have more questions in this context than I do have answers but these are questions worth the commission's time in considering, I believe.**

**Does research include both control of the independent variable, control of the dependent variable and implementation of data collection systems that measure both?**

**Does research only include the implementation of the data collection system?**

**At what point does the university based researcher become responsible for independent variables over which there is only outside or community control?**

**And if university-based researchers become responsible for independent variables for which they have no control and are prevented from implementing data collection systems that would otherwise provide information to improve the independent variable, is there a loss of human rights or induced protection for participants in that broader intervention?**

**(Slide.)**

**These bring up some issues around standards,**

**I believe, for informed consent. Within the context of the example I was just describing, we were almost prevented completely from having a partnership at the University of Kansas with community members who were very interested in using the Youth Risk Behavior Survey.**

**The Youth Risk Behavior Survey is a standard data collection instrument, a standard survey that is used among youth throughout the country. There are standards for its implementation that are laid out by the Centers for Disease Control, which developed the instrument and is using it principally throughout the United States themselves, and which community wanted to adopt and requested that we provide some support for in the form of analysis of the data.**

**Now on one hand one could use the current regulations to say, well, basically this is a community intervention that is outside the scope of university research and it is outside the scope of the individuals who are conducting research on behalf of the University of Kansas. It is data that is already extant and so it is exempt according to the regulations on the one hand and yet there are IRBs, and I understand this is not a unique case in the United States from colleagues of mine throughout the country that want the university researchers themselves to have control over the independent**

**variable and t implement a higher level or a higher standard of informed consent as a result and we were almost prevented from that partnership -- that important partnership at a community level from just simply doing the analysis of the IRBS data because the IRB wanted specific written informed consent by the parents and guardians.**

**So must researchers take responsibility for the intervention in this context or just data collection system which they implement or may not even implement themselves?**

**To what extent do IRB reviews by grant making agencies serve to protect participants and does it cover the responsibility shared by these researchers and community implementers or does it serve to only review the intent of the grant making agency?**

**And, finally, does informed consent or should informed consent include only those procedures for which the writer of the statement has responsibility but is this inadequate protection for community participants?**

**(Slide.)**

**And then a couple of other issues that are emerging within this context. One, it has come up over and over again within the context of implementing an IRB in my eight years experience that**

**local IRBs are often used by institutions as review committees to protect the institution from law suits rather than their original intended purpose of protection of participants in research.**

**This is not -- this should not be a standard, I do not think myself, that it should be held to but it should be something that is discussed within the context of the regulations and suggested in the context of the regulations.**

**It limits the ability of researchers to engage in more ecologically valid research resulting from more egalitarian partnerships between university based researchers and community based program developers and implementers.**

**Is there such a thing as community informed consent? Should the community itself be the standard by which these kind of relationships and these kind of interventions really are implemented?**

**In many communities throughout the United States there is a different level or different consideration of what is the individual versus what is the community, what is the family make up, et cetera, and I think regulations would do well -- the commission would do well perhaps to consider some of those different conceptualizations of individual, family and community in light of the regulations, which principally touch on individual based**

**protection. And is this different from traditional individually based informed consent?**

**(Slide.)**

**Finally, I have got several recommendations. Please take them in context and they are literally just recommendations and could be subject,like anything in my experience, to selection bias based on my own experience.**

**But a redefinition of research to include innovative university-community relationships, I think, would be in everyone's interest.**

**Make explicit in the regulations or in commentary how informed consent applies in this context, e.g. limiting university IRB review to procedures for which the personnel are clearly responsible while still protecting participants from possibly harmful procedures.**

**Strongly advocate for the minimization of legal liability by the university as a standard by which university-community relationships be judged.**

**And then, finally, make sure there is as single national standard. Not just a standard that shifts depending on which federal agency is reading the regulations. There has been in my experience, especially in the past several years, that a variety of agencies are starting to make policy judgments or suggestions to local IRBs that are putting IRBs in a**

**position where they have got to make decisions based on very conflictual agency readings of the rules and this really should not -- the IRB should not be in that position.**

**Thank you very much.**

**DR. SHAPIRO: Thank you. Why don't we just see if there is any clarifying questions? We will hold most of the questions until we have heard from our second guess but if there are some clarifying questions we could take them now.**

**Larry?**

**DR. MIIKE: Are you asking -- a couple of questions. Are you asking us to consider research -- the definition of research as a parsed out definition? To me, research is the entire project. You cannot take a piece of it and say that is research and this part is not. And then the other thing second is that the relationship between the university and a community in a project where you have multiple interests and multiple leaders, and you know you have been to our's, you know it is pretty common over there, isn't that much like the multicenter clinical trials now where there are battles between individual IRBs and they may differ? Isn't that the analogy that we are looking at and isn't there some kind of common solution to those two situations?**

**DR. FRANCISCO: I do not know if there is a common solution. I think the analogy may hold. I have not really thought about it from that point of view. I think the style of research is a bit different but the actual practice, the actual struggle might be very similar, and the kinds of questions that are raised may be similar.**

**With regard to a definition, I am not interested -- I am not advocating for parsing out of different kinds of research as much as a recognition within the context of research that there are a variety of different interests that are at play and that there is a different relationship that is emerging where different parties have different levels of power in the context of that research.**

**DR. MIIKE: But I take your recommendation to say that the university IRBs should just look at what the university is involved in and they should not be second guessing what the community side is doing in the research. And I do not find that tenable because they should be concerned with the overall research project and it is a question of the university -- you people, university, and the community to find some common solutions so you can satisfy both sides.**

**It is not a question of we will only look at this little piece here even though it is within the**

**context of a larger piece. I think, to me, that is an unsatisfactory solution.**

**DR. FRANCISCO: I agree with you. That is an unsatisfactory solution and I am not sure that I have any answer for it at this point. What I am suggesting is that the relationship be looked at and that maybe some recommendations be made for how it is that universities and communities might want to consider dealing with those tensions, dealing with the possibility that a university could coopt perhaps a community and say, you know, you really should not be doing this kind of research rather than allowing for a more egalitarian process in which they can figure out how to work out their differences.**

**I am not saying that there should be a prescription on that as much as there should be a surfacing of the issues in this context so that the university is not sitting there and saying, no, we are the only standard that is discussed within the regulations or within the context of some national commissions that should be held and that there should be a process that perhaps the regulations or interpretation of the regulations should include telling the universities that they really need to figure out a process for dealing with some of those issues so that the relationship is acknowledged.**

**DR. SHAPIRO: Than you. Any other**

clarifying question before we move on to our next guest, Professor Trickett?

**EDISON J. TRICKETT, Ph.D.**

**PROFESSOR OF PSYCHOLOGY**

**UNIVERSITY OF MARYLAND**

**PROFESSOR TRICKETT:** I just wanted to make a couple of comments on the previous question. There are those who raise the issue about the institutional composition of IRBs when community research is involved as one way of thinking about it and, also, having as part of the application process or instead of the -- altering the composition of committees, some kind of statement of community representation and buy in, agreement or whatever with the -- with whatever the project is.

I mean, there are ways that people have started to think about that kind of issue behind your question in terms of the structure of IRBs and the requirements on people conducting community-based research as presented to IRBs.

**DR. SHAPIRO:** Thank you, Professor Trickett.

**PROFESSOR TRICKETT:** Let me join Dr. Francisco in expressing my appreciation for the opportunity of speaking with you. What I have done for most of my career is conduct community based research primarily on the nature of school environments and how through their policies,

opportunities, structures, norms in relationship with parents they affect the well being of adolescents, the development of adolescents.

For the past decade I have focused on how schools process students from different cultural backgrounds. In recent years conducting research with my wife on the acculturation and adaptation of Jewish refugee families from the former Soviet Union.

Throughout this effort, I have been interested in issues of process between outside researchers and insiders in various communities. For example, 20 years ago I interviewed all of the principals of public schools in New Haven, Connecticut, about their experience with social science researchers to try to figure out how people like me were perceived, how we acted, the relevance of the information we provided in terms of feedback and so forth. Just generally how they construed the nature of the research relationship between scholars and community institutions.

I am also currently involved with the National Institute of Mental Health on two projects related to the conduct of community based research. One involving ways to increase the community impact of interventions in HIV/AIDS and, a second, a book on models, dynamics and issues involved in developing collaborative relationships with community groups and

**institutions.**

**A recurrent theme involves the importance of attending to first the community context within which our work occurs and, second, the need to focus attention on the kinds of research relationships we develop with community institutions and individuals.**

**It is from this background that I approached the issue of ethical issues in community based research. My experiences have suggested that community based research often involves quite a different paradigm of the research enterprise than is covered by the current Code of Ethics in psychology, which emanates from a laboratory tradition of research and a doctor-patient tradition of practice.**

**I want to mention half a dozen different areas that I think are -- have emerged from my own work. The first, seemingly simple but often ignored, is that community based research has community consequences. That is it has ripple effects in the communities where it occurs and these ripples relate to local community concerns, past experience with outside researchers, the history of race relations in research as manifestly evident in the Tuskegee experiment, and numerous other factors unrelated to the content of the research per se.**

**Thus the degree to which intervention research implications -- intervention implications of**

**community research are anticipated and followed is one area of ethical concern. That is we cannot disentangle the research from the community context in which we carry it out.**

**Secondly, community based research often involves the infusion of temporary resources from the outside into a community often in the form of external funding. Much community based research involves work with relatively disenfranchised groups who can use such resources to provide local employment, community credibility in the service of their own local agendas, et cetera, et cetera.**

**The community implications then of what happens when the grant runs out becomes important as well as the meaning of informed consent in populations where outsiders have resources to offer.**

**Third, community based research is increasingly being conducted with culturally diverse populations, whose circumstances and traditions interact with ethical business as usual. In the informed consent domain, for example, increasing work is being conducted with refugee populations, many of whom, such as Bosnians and Cambodians, have had extremely traumatic histories involving government sponsored terrorism.**

**While it is vitally important to understand their situations, it is difficult to assess how**

**freely they may give informed consent when their history suggests that governments and other official representatives are often to be obeyed or else.**

**The ethical issues involving translators, for example, becomes important to consider as it involves assurances of confidentiality. So that as the domain of populations increases, the sort of specific -- situation specific issues related to work with them becomes very important.**

**Fourth, such cultural differences between insiders and outside researchers has been one factor leading to a reconsideration of the research relationship emphasizing community collaboration.**

**Collaboration has been touted as a value on epistomological grounds, that is the more reciprocal and co-equal a power relationship between researcher and citizen, the more likely the data will be valid and community buy in authentic.**

**It has been touted as a means of reducing the distance between scientists and practitioners and so forth but collaboration raises its own set of ethical concerns. For example, using indigenous data gatherers not only increases the salience of the issue of confidentiality of information. Do I want to reveal sensitive information to someone in my community rather than to an outsider? It also raises the issue of who the community is in terms of**

**the inclusion as collaborators. These are not simple questions.**

**Fifth, community based research also has been a forum for increased interdisciplinary collaboration, particularly in the service of social and public health issues, which no single discipline can claim as their own. The ethical codes of these disciplines are themselves in some conflict around emphasis. For example, anthropologists are more ethically bound to contribute to the communities they study than are psychologists in terms of the existing codes of ethical conduct.**

**Wax in 1980 commented on field work as posing a kind of challenge in contrast to bioethical -- biomedical procedures. "Field work," he says, "Is a complex relationship, interaction between researcher and hosts and is constructed in process of give and take and so it cannot be assimilated toward the model of biomedical experiment where the researcher is free to outline what is to be done to the passive subjects."**

**In biomedical and psychological experimentation researchers approach their subjects with definite plans of activity and inquiry. Since these may affect subjects in crucial ways, a persuasive argument can be made that the informed consent of the subjects should be solicited prior to**

**the experiment. Otherwise they should be free not to participate.**

**When consent is solicited, the subjects are treated as autonomous beings valuable and competent in their own right and the scientist is freed from any unit of authoritarian or coercive conduct.**

**In ethnographic work, however, where the goal involves understanding complex naturally occurring cultural patterns of behavior, the dynamics of the inquiry can be scarcely set beforehand but must be constructed within the field. Under these circumstances, consent becomes a negotiated and lengthy process rather than a once and for all event.**

**Needless to say the conventional consent form is so irrelevant as to be a nuisance to all parties.**

**In addition, particularly with respect to the increase of ethnographic and qualitative work in community based research, situations arise which cannot easily be resolved by currently -- by current shared ethical understandings.**

**Bob Trotter, an anthropologist, recently mentioned a situation involving a research study in the AIDS area where an ethnographer was conducting participant observation in a place where sexual encounters occurred. The ethnographer knew that one of the individuals was HIV positive and knew that**

**this individual was not telling his potential partner of his HIV status. The risk to the partner was, of course, palpable. The ethical question was what to do. These kinds of situations suggest that community based research across disciplines confronts unanticipated situations where ethical issues are obvious but resolutions are not.**

**Finally, community based research involves ethical issues for investigators in terms of the potential risks they ask of individuals working for them on the research itself. Pat O'Neil, for example, reports on a case involving the naturalistic study of child abusing families in their homes. The ethical question is how much and what the research assistants should be told about the study and the people whose homes they will visit. Should they be told the study involves child abusers? Have they right to know that they are going into the home of a convicted child abuser?**

**If another instance of abuse occurs while they are in the home they may feel compelled to try to intervene putting themselves at risk. Even if they do not intervene they will be proximate witnesses to a violent crime and the offender will know that the crime has been witnessed. Such a situation places a witness in danger.**

**The less the assistants are told, the less**

**they are able to make an informed decision about the risks they run but the more they are told, the more the data collection is potentially compromised.**

**So in these and many kinds of community based situations community based research is forcing a confrontation with new ethical issues relating to new professional roles, an increasingly broad range of populations and disciplines involved in the process, a reconsideration of the research relationship in a more collaborative direction, and the need to attend to the situation researchers place members of the research team in.**

**Together they signal something more than minor revisions of current codes but rather a more dedicated effort to understand community based research in its own right.**

**Like most academicians, I am probably better at posing problems than offering solutions. However, at this point in the development of community based research I am not sure that solutions are, indeed, solutions.**

**My understanding from my colleague, Ken Pope, is that ethical issues only become crystallized in a profession after years of experience have accumulated and individuals involved have begun to develop some consensus about what they are.**

**Thus my current belief is that creating**

**processes for exploring the kinds of ethical concerns which have surfaced in community based research is the immediate task and central to furthering our understanding of what we have gotten ourselves into in the first place.**

**In my work with NIMH on collaborative research relationships we are doing just that in terms of interviewing community based researchers around the country about what they have confronted.**

**In addition, there are steps which external funders can take to ensure that structures are available in community based research to allow an exploration and surfacing of ethical issues as they arise. The development of interdisciplinary groups to focus on ethical issues in community based research is also a priority.**

**Thank you.**

**DR. SHAPIRO: Thank you very much.**

**Let me now turn to the commission for questions, either clarifying or otherwise, for either one of guests here today.**

**Alex?**

**DISCUSSION WITH COMMISSIONERS**

**PROFESSOR CAPRON: Is otherwise obfuscating?**

**DR. SHAPIRO: I hope not.**

**PROFESSOR CAPRON: I want to get your collective help on trying to focus what you think the**

commission can do, and let me put forward several alternatives. Professor Trickett just suggested a partial answer to this, which was that what we should do, I suppose, is to -- perhaps a vehicle for disseminating a statement of what some of these issues are and ethical concerns, that it is premature, however, to expect that there would be ethical solutions and it would be sort of beside the point to address them by, as you put it, tinkering with the regulations.

And I would like to ask you and -- on the other hand, Dr. Francisco did have some specific recommendations for us. It seemed to be to modify the regulations in part to remove from the research category, at least the university based part of that and the IRB review, responsibility in certain areas.

And it struck me that one of the issues that I would like you to respond to is in deciding what this term community based research encompasses because I have heard at least three different things today.

One, research which could be observational, it could be interventional or whatever, but is community based in the sense that it occurs in a naturalistic setting that is other than a laboratory setting. So it could be psychology or sociology or anthropology in the community rather than in a

**laboratory.**

**The second definition of community based research is research which affects a community. An intervention which is aimed at altering the circumstances of life for people and in the paper that Dr. Trickett gave us, you addressed that, and I think the question there does come closer to the issue of other regulatory response. Do we adequately attend to the issues that arise when an intervention affects a community? How do you get permission or consent in that process for something that is going to willy nilly affect members of the community?**

**And the third is something which I had not heard before, from Dr. Francisco, which is the notion of within a research project that certain other things that are going to happen are determined by the community, are outside terms of negotiation with the investigation. They are not something the investigator is bringing to it but somehow the community collaborators are doing something, which is different than the second category. It is not an intervention being tested for this purpose. It simply is somehow the conditions.**

**And it is that latter category which clearly, it seems to me, there has to be some sort of regulatory response to if it is, indeed, a distinct category. I am just not quite clear with examples of**

what falls into that.

So I would like to know are these three separate categories? Are there other categories that you would see? And, if so, as to each of these could you give us any further guidance as to what you think this commission can do in responding to the concerns that you have raised?

PROFESSOR TRICKETT: After you.

DR. FRANCISCO: The three categories seem quite inclusive of what we have discussed. I am not specifically sure what the commission could do directly. I think the biggest -- probably the biggest step forward that the commission could make is to really recognize that third category and the kind of relationships that are inherent in that and the possibilities and potential pitfalls that could be inherent within that context.

I think Dr. Trickett is excellent in raising some additional issues beyond what I spoke about within that context and there are no easy solutions, I do not think, but I think the possibility for mechanisms by which those questions could be raised and answered at a local level could be suggested by the commission.

I think it would help folks out at my level, both as a participant and a member of an IRB within a state university, as well as someone who is a

**community based researcher in these kind of -- the third category of -- mostly in that third category of researcher, who does partnerships with commission organizations.**

**Most of which are really funded by foundations and secondarily by state agencies and a few federal agencies in which communities really are putting together interventions that are vast experiments in social engineering.**

**PROFESSOR CAPRON: May I follow up with one question to each gentlemen?**

**I guess I am not clear then as to how the difference in the second and the third category -- the second category being when an intervention is tested and the community based means that it is being used in the community rather than necessarily person by person. Versus what you are calling the community aspect of community-university collaborations where it is -- by implication, it was the university aspect that was the experimental, I thought.**

**DR. FRANCISCO: Well, more clear --**

**PROFESSOR CAPRON: Can you give some more examples?**

**DR. FRANCISCO: Absolutely. In the second category that is the more common kind of research that goes on, I think, in general between universities and communities. Where researchers at a**

university might come up with a mentoring program, might come up with some sort of an intervention like mentoring after school reading programs.

Programs like the wonderful situation in Kansas City where some folks decided that they were going to raise the question and do a social marketing campaign around is it good for the children, and they were going to implement that and try to get everyone to use that standard -- that question as a standard for every decision made at the community level.

There were a tremendous amount of games that were created. It was a wonderful intervention that was really principally implemented by community folks and developed and implemented by community folks in which I had a part to play.

PROFESSOR CAPRON: How does that differ than the second category? It seems then it is simply the input as to what the intervention --

DR. FRANCISCO: They are coming up with the -- they are coming up with the intervention. Most -- in the second category the university is coming up with the intervention and it is a researcher that is university-based coming up with the intervention.

PROFESSOR CAPRON: But if the researcher from the university is going to collaborate -- I mean, in other words, somebody in the community says, "I think X, Y, Z intervention, mentoring or

redesigning the streets to make them safer or whatever would be a good idea and there is community enthusiasm," and someone in the community says, "Well, you know, before we do this all over town or all over the state or something, maybe we ought to figure out if it works and there are some scientists at the university who are good at measuring things."

And they go and they sit down and they say, "Could you help us figure out whether this is, in fact, better than what we are doing now?" And they say, "Yes, we can design that," and they design it together.

At that point, although the intervention has come from the community, why should it be treated any differently than something which somebody in the university happened to think up? I mean they are collaborators now and the usual rules about the research process it seems to me ought to apply equally to that as to something that was in the second category. I guess I do not see the difference.

DR. FRANCISCO: I do not now that they do because the person who is representing the university has virtually no say in what is going on within the community.

PROFESSOR CAPRON: Well, they have a say as to whether or not they collaborate.

**DR. FRANCISCO: Oh, absolutely. That is not what I am saying. What I am saying is over the intervention itself, over control and implementation of the intervention itself they have got no say, which is probably, you know, just as well.**

**PROFESSOR CAPRON: Right, I understand your point. As to whether or not it convinces me it is different is -- for the -- if you go back to the first category which you, Dr. Trickett, spoke about. To what extent are the kinds of things that we could do in this area basically a matter of reporting and discussing the considerations that arise so as not to change regulatory responses or even maybe you could change what IRBs do but simply to make people aware of these as issues?**

**Certainly some of the things that raise strike me as really not being very distinctive to community based research. I mean, the concern that your researcher could be in a position where he or she could be in danger or could be observing a conduct which might give rise to their ethical obligations to report child abuse or something, or is aware of the sexual status, the HIV status or other of one sexual partner and not another.**

**Those are issues which clinicians doing clinical research face as well. I mean, the person who is doing research on children in a children's**

**hospital and who finds a parent or a guardian who is battering a child and observes that happening faces the same set of issues and ought as a part of a training process to be aware that the issues could arise, and what is the response that is expected of a person there.**

**There was just reports of this ongoing study in Uganda, I believe, of what are called the discordant HIV couples where the researchers observed the conversion rate in the seronegative couple -- pair of the couple and it was criticized. It was praised by some people as very valuable research and criticized by others because the researcher aware of this was not intervening beyond making the method of safe sex available to them and so forth but was not otherwise intervening, et cetera, et cetera.**

**I mean, so it seems to me that these issues, whether you call them community because they happen to occur in the community or not, are not so distinctive but it still could be valuable to the extent that we want to mention them. I do not see them as being issues that are unique that deserve special treatment, however.**

**PROFESSOR TRICKETT: Let me just ask a question related to that. One of the things I thought of when you were talking about the clinician example is that it is clear to the clinician who the**

**client is, I think.**

**PROFESSOR CAPRON: Well, I mean, in this circumstance you may be studying in a pediatric setting X, Y, Z pediatric issue but some of the children will occasionally come in for their appointment and show evidence that they have been injured.**

**Now the researcher at that point has a clinical relationship -- I mean, a research relationship with the child but suddenly a potential issue vis-a-vis the parent who has maybe consented to the child being there but is now going to be facing an issue, well, I have got to turn you in for child battery.**

**Now it may be more acute when it happens in the home because the researcher is out of her own or his own milieu and at that moment is exposed. If they take an action, you know, they are more physically at risk but the issue of the conflicting role -- I mean, I have been brought into a private relationship, I now have information which could be harmful to one party in that relationship but society expects me to act on that to protect the other party and so forth.**

**I would expect if I were running a research program and it involved social psychologists or anthropologists in the community or it involved**

**pediatric residents I would want to give them each an education fairly comparable about what you do under those circumstances.**

**It does not seem to me that one is, in principle, different from the other, although the details of how you respond are nuances that you would want to attend to.**

**I am trying to look at what is distinctive about the community aspect here.**

**PROFESSOR TRICKETT: Right. One of the things that I -- I am not sure if this covers -- this is a very useful kind of discussion of different kinds of examples to see where the commonalities and differences lie.**

**One of the issues in the participant observation AIDS example that I gave was that under those conditions -- this is not someone with whom you have a research relationship in the sense of having informed consent to look. So that may or may not be a difference in terms of the structure of the relationship between the researcher depending on the method.**

**One of the things I wanted to mention was different methods highlight different kinds of problems as well. Now that may cut a -- that may be distinctive to community research but what has happened, I think, is that being placed in certain**

**kinds of situations has heightened issues that may, indeed, be relevant to other areas that have not surfaced in those areas.**

**So the dialogue may be, in part, one of seeing where the commonalities lie and where the differences lie and this sort of emetic distinction that anthropologists make about the general and the culture specific.**

**PROFESSOR CAPRON: Thank you.**

**DR. SHAPIRO: Larry?**

**DR. MIIKE: Perhaps I should use a concrete example from Hawaii in response from Dr. Francisco. To me the issue about research -- community research is the issue of the client before they give consent insisting on you changing your research design or having a great say in it as opposed to a clinical trial where you explain the risks and benefits and they do not really have a say about what the actual drug is going to be administered or whatever.**

**And I will give you a concrete example. My wife is involved with a Hawaiian community who has an unused playground, et cetera, and very low job rates, and they are trying to see a way in which you take the community resource, which the city is willing to more or less give it to them, but to turn it into some kind of enterprising activity. A laundromat or something like that.**

**The university researchers are looking for communities in which they can study empowerment issues so they come in and say, "We would like to work with you about empowering communities." But the communities already have their agenda and they know what they want to do but the university comes in with certain requirements and the community says, "Now wait a second. It was our idea in the first place. We would like your help with the data, et cetera, but you do not tell us to change our study because it has to fit some kind of research design."**

**So I think -- I guess, to me that is the nutshell of the difference in community directed research and the clinical individual oriented research.**

**The representatives of the community are giving consent. They are influencing the research project but they are not giving consent for individuals. If you are going to go interview somebody you have to get their consent but the giving consent for the researchers to come in and look at the process that the community is going about to try and enact change.**

**I am stating that as a given but I see you shaking your head so you would generally agree with me that that is the crux of the difference.**

**PROFESSOR TRICKETT: And part of that is the**

**degree to which one can specify beforehand what one is going to do.**

**DR. MIIKE: Right.**

**PROFESSOR TRICKETT: And whether or not there is a need to specify beforehand rather than -- before you can start something. You know, it is like you need credit before you can get credit. You know, you need to have IRB approval before you figure out something that you want to present for IRB approval. It is just one of those kind of things.**

**One of the things I wanted to just mention in the spirit of our previous short conversation was that I do not see any value in necessarily touting community based research as a totally different animal than other research.**

**What I think is missing a conversation about the large amount of tacit knowledge that people doing community based research have about ethical issues and finding forums to surface that so the conversation can occur about similarities and distinctiveness as it relates to the three different kinds of community based -- meanings of community based research as it relates to the different kinds of methodologies that are now being commingled in community based research. That is my perspective on it.**

**DR. SHAPIRO: Diane?**

**DR. SCOTT-JONES: Part of my question has already been captured in what Larry just asked. The rest of it has to do with what you see as the risk of community based research. Are there risks related to the -- well, let me just stop there. What do you see as the risk of community based research that we should be concerned about as we are working on our report?**

**DR. FRANCISCO: Well, let me -- if I could lay out one while Dr. Trickett is thinking about a few others. There is -- one risk, I think, is this issue around individual informed consent and the role that that ends up playing in these interventions that are conducted by community groups. Let's say a community partnership or a community collaborative.**

**And if, for instance, in the context of a university that has to get a certain kind of written informed consent, a fairly tight sort of -- tight informed consent that includes description of the independent variable for which he or she may not have any control could end up being prevented from occurring.**

**The research could -- well, the intervention I should say, not necessarily the research, but the intervention could be prevented from occurring in a situation where the community desperately needs that intervention and because of a university liability**

**issue or because of a standard for informed consent that is based on really other different kinds of research that engender different power relationships where the individual -- there is an individual researcher in an individual person that is involved in the relationship that is not present in a number of community settings where it is really a community that is speaking on behalf of its residents, who might be experiencing tremendous amounts of poverty and all that goes with it. Interventions would be done by folks within those community settings that could be prevented from occurring if researchers have to take also responsibility for those interventions themselves when the real responsibility is for a data collection instrument.**

**And I think there could be -- there could be potential harm inflicted on that community and residents of that community for the lack of intervention as a result of a kind of approval that might not be relevant for the intervention to take place that university could force on it in a relationship that is not appropriate.**

**I hope that was clear. A university could partner perhaps with a community group, let's say on an Indian Reservation or in a community of fairly limited power. I was in a situation once with the Hickory Apache Tribe where there was an outside**

**agency that was funding us and funding this community intervention, decided that a certain kind of intervention was warranted on this Reservation, decided to pull funding because the Tribal Government said to us, myself in particular as a researcher, that you cannot use surveys. "We have been surveyed to death. You cannot use surveys."**

**This outside funding agent decided that if you are not going to use this particular kind of survey in this context that the intervention itself was not -- that it was part of the intervention to be able to use this survey and that if the survey was not being used then they were going to pull funding on this project.**

**As a result, they pulled funding on myself and pulled funding on that project, and I think that the -- I think that the community was adversely affected by it when the data collection systems that we put into place and negotiated with those community members were as wholly effective at documenting the effectiveness of that particular independent variable in other situations.**

**Now this is not a case where a university IRB was making a decision but a foundation -- but a funding agent was making a decision.**

**DR. SHAPIRO: Is that an argument over ethical treatment or is that an argument among**

**scientists regarding what is an appropriate intervention?**

**DR. FRANCISCO: Well, I think the ethical treatment is the outcome that occurs from that relationship and in this case I think people's lives -- in this case there was a high rate of suicides and a high rate of drunkenness on this Reservation. And I think their lives were minimized as a result of their pulling of this intervention.**

**DR. SHAPIRO: Arturo?**

**DR. BRITO: I was actually going to follow Diane's questions about the risk more related to the community on the findings but I want to address this issue here. What -- in your suggestion about the new definition of research or your discussion of that, one of the things that concerns me is related to what you just said, is that you mentioned that an intervention may be desperately needed by a community.**

**Are you talking about an intervention that -- once again if an intervention is known to be desperately needed by a community then it is truly not research. Or are you saying that you are posing a question that something may be desperately needed by the community? Do you understand what I am getting at?**

**DR. FRANCISCO: I sure do.**

**DR. BRITO: So one of my concerns --**

**DR. FRANCISCO: Absolutely.**

**DR. BRITO: -- is about the definition of research with community settings, and I do some partnership with the community from the university and I am aware of these, is that often more harm comes from defining things that are not truly research as research and making general statements for a community from the outcome -- outcome measures that are used in there.**

**So I am -- I am just -- once again I worry about what is defined as research by the community and when issues arise where intervention is theorized to be needed by the community that it should be done in a standardized research manner but -- so to --**

**DR. FRANCISCO: I think you are starting to get right at the heart of it and is it research or is it not research as described by the regulations.**

**DR. BRITO: Right. So instead of saying --**

**DR. FRANCISCO: Many folks are describing it as research when it is really an intervention that is a community intervention that is desperately needed and some help with clarity in dealing with some of that issue through the regulations, through interpretations of that, I think, would help.**

**DR. BRITO: Okay. So my original question is I would like to hear more about the risk that you**

**foresee for communities from the findings of research or from findings of what is interpreted to be research and what your experience has been with that.**

**For instance, stigmatization of certain communities, less resources being made available to communities because of a finding from that research, and I would like to hear a little more discussion about that.**

**PROFESSOR TRICKETT: In the paper that one person referred to that I did a while ago, I talked about the Barrows, Alaska, issue where a survey of alcohol use and so forth in a particular Inuit community made the New York Times in which the community was labeled a bunch of alcoholics. Clearly the kind of community implications from that publicity from the media use of findings or interpretation of findings is one area there.**

**There are a couple of things I wanted to mention with respect to Dr. Scott-Jones' question and I did not. One, I think, and this has to do with the potential downside, the risks.**

**I think one is the risk of being essentially a community pollutant, of interfering with ongoing indigenous community dynamics in a way that you are unaware of because you do not understand that your research in a community context is an intervention, whether or not you like it to be. So I think that**

**is one kind of thing.**

**The second involves the false expectations issue or the false hopes issue around the degree to which most of the work that is done in communities is time limited where the strings are really not pulled by collaboration but by the kind of external funding that Dr. Francisco is talking about and sort of thinking through the risks of creating both -- not necessarily harm to individuals in particular experiments but perhaps harm to social science was the real risk there.**

**And the third is -- in a lot of studies involving things like preventive interventions there is a risk of not knowing what you are doing to the people you do not include in those interventions. Parents of kids who are labeled at risk who are given certain things, talking to other -- you just do not understand the ripples that you are causing with these kind of things, and so my -- my concern about the risks is not a specific set of risks but try to focus on processes that can identify the kind of risks that over time can become a kind of database for developing ethical issues, which makes some generalizable sense.**

**DR. SHAPIRO: Okay. Diane, you want another question. Alex, then I have an observation, and then we will let Marjorie close this part of our session.**

**DR. SCOTT-JONES: Okay. This is a follow-up to the question that Arturo asked. He mentioned as he was talking what is defined as research and I would like to hear you say a little bit about that because it does seem that part of what you are talking about is actually meeting the needs of a community for services, for programs and so forth, and it could be the case that the sources of funding for those programs require some documentation that the program was run effectively, and I suppose that gets labeled as research.**

**But could you say a little bit about the definition of research and boundaries that we might usefully set in our work between research and say the evaluation of a program or the evaluation of services to a community?**

**DR. FRANCISCO: I think often times at least at the IRB level research is really defined as anybody collecting any information for any purpose and I think it is a little bit more complicated than that.**

**And we have -- within the IRB that I have been a part of for the past eight years, that is really what it comes down to is research every time we collect data for whatever purpose it might be? Or is that really part of the intervention? Is the data collection itself and the implementation of a data**

**collection system in a given context really part of the intervention and is outside the context of research and then exempt from IRB approval?**

**And that is, I think, something that folks in the field could use a little help with and in our IRB they try to be much more inclusive and more times than not they come down on the side of every data collection possibility is research and it is a lot more complicated than that. It is an ongoing argument within our IRB and it should be there but I think a commission like this could also inform and help enlighten by bringing those kind of issues to the fore.**

**DR. SHAPIRO: Thank you.**

**Alex?**

**PROFESSOR CAPRON: I want to suggest that it would be most helpful to me and maybe to the other commissioners if as a result of this discussion today the staff were to attempt to do two things. First to provide a short taxonomy of community based research and in addition to the three categories that were enumerated before of research which is conducted in a naturalistic setting, research in which the intervention is being applied on a community wide basis, research in which the researcher -- I now understand that third category a little bit better where the researcher -- the research intervention is**

**the study of the effects of some independently applied intervention.**

**And the -- the fourth is research, wherever it is conducted, that may lead to generalizations about a community. We, indeed, saw this when we were studying the human biological tissues and we said, "Well, if you are going to come out with characterizations that people in a particular group of some sort, whether it is called a community or otherwise, have certain characteristics then there may be some need to attend to that effect." To see do you have to state your results in that way, which can be then misreported or exaggerated or others. And if you do, it if is a legitimate thing that you are looking at, have you gone through some process that allows community input on that in advance?**

**And it seems to me that there may be other categories but I would like some taxonomy.**

**I want to be clear having said that I now understand a little bit better what that third category is, I want to again without saying that it is not useful to describe it that way, to suggest to you that there is a parallel and then I would like the staff particularly to look at this issue.**

**There is a parallel with the claim that is sometimes made in clinical research, such and such a practice has been ongoing. Maybe one practice in one**

**group, one practice in another. What the researcher wants to do is to evaluate what the effect of those interventions are.**

**And the researcher would say, "The only thing which is research in what I am doing is whatever interventions I am using in the evaluation process. So that if I am using an x-ray that has one level of risk. If I am using a small blood draw, that has another. If there is risk in data, privacy risks or whatever, that is what I am doing. I should not be held responsible." And this is what I took to be in the end your point, Dr. Francisco. "I should not be held responsible for the level of risk that is inherent in the intervention which is already ongoing."**

**And I want to know if we have in the literature any considered evaluation of that as an argument so that a researcher who comes before an IRB and who wants to say in deciding whether I need consent and what I need consent to, and in deciding whether the risks and benefits are appropriate and so forth, all the IRB should be looking at is the evaluation methodology that I am using and not holding me responsible or that clinical intervention or in this case that community intervention that is independently being applied.**

**In a way that is parallel to an argument**

**that Bob Levine has made forever about why we should not call things therapeutic research because part of what he has always said is that what we have to do is disentangle the intervention from the research aspect of it and the fact that it is research is what is important to remember but labeling therapeutic does not add anything even if there is an intervention with a potential therapeutic value in there.**

**Anyway, is that task clear and does it seem reasonable that you would come up -- because I think that is what I get out of this panel that we would potentially see whether there is anything.**

**Even if it turns out -- it may still be useful to tease out some of these problems and to use illustrations from both areas of science to show why there is an issue or what the researchers or IRBs can do in response.**

**DR. SHAPIRO: I think, Alex, your last comment, if you do not mind me intervening here, is, I think, consistent with something I wanted to say and then turn to Marjorie to close this particular section up.**

**And that is on the issue of whether the intervention is independent or not depends, of course, on what we mean by independent. If it is already ongoing and unrelated to anything you have ever done or ever thought of, that is one thing. If**

**not, it is a totally different matter.**

**My own reaction -- one, I want to thank you both for your very helpful remarks and some of the insights that you have shared with us. It is -- my reaction to it is that those of you working in the community-based research really see things in a new light as you -- as to be expected, which helps clarify issues which come up in the other side too, come up in the biomedical example, too. It is just that you find some new ways of thinking about it, which provides insights to us and it is extremely helpful and this really speaks to the conversations that you suggest that we might have to clarify these issues.**

**Just to take one which you outlined, one I think of the seven or so characteristics that is there is a temporary infusion of resources, which might make people temporarily better off. That sounds very familiar to something we were discussing this morning regarding what you might owe a participant in a trial when the medication turns out to be successful and then they lose access to that medication. It is really a similar kind of problem, although on a quite different format and may require different solutions. But I really do think that the experience you have shared with us is really extremely helpful in helping us look at this overall**

**even though we might think in the end in some of these cases we can help each other by this interaction which I think is what both of you were saying.**

**Marjorie, let me turn to you for some concluding remarks.**

**DR. SPEERS: These remarks may have been more helpful if they had come sooner rather than later but let me say them anyway.**

**The commission, I think, has a unique opportunity before it and that is as we are looking very comprehensively at the oversight system, one of the criticisms that has been made of the current set of regulations is that it is very much focused not only on individuals but also on individual investigators, individual institutions.**

**And in a sense no where is that clearer than when we look at community-based research. And if we think a bit about community-based research there is at least two trends that I think are important to point out. One is that much more community-based research is being conducted now than it had been in the past, that it is clear for certain kinds of interventions -- and I am thinking primarily of the health field, not so much of social science although this would be true in social science, but in the health arena many interventions are now being tested**

**in communities or at the population base level rather than simply at the individual level or in the clinical setting. So more research is being funded and conducted in communities.**

**The other trend that we can really trace back from the early '80s is that the community has more and more responsibility and control over the research. When we think about the studies that were done that were funded by the National Heart, Lung and Blood Institute, the first primary prevention cardiovascular disease prevention trials in communities, those were very much research studies done in the community, not with the community but in the community. The researcher had a protocol, went into the community and intervened.**

**And part of the reason that those trials may not have been as successful as they could have been is because they did not involve the community. They were not done with the community and so we are seeing more research done with the community and that has brought up a number of issues. Some of them that were discussed today.**

**For example, when a community collaborates and is designing the study or has access to identifiable data, is that community then in some sense a performance site or a collaborator in the research? Do they need a single project assurance?**

**Do they have to have an IRB to review it? How many IRBs are going to review the study? And you get into those kinds of issues.**

**As you -- in community research as you move from individually focused to population focused research a number of questions come up about informed consent. There may not be the possibility of getting individual informed consent depending on what the intervention is.**

**Certainly for educational interventions this may not be a -- for an educational intervention that involves little risk, assuming we can judge that risk, the informed consent issues may not be as significant as they are in an intervention where you might be considering releasing a genetically modified vector to control an infectious disease.**

**So, you know, we are talking the whole gamut here.**

**What I hope that we have gotten out of this session today is a sense that this is an area that is growing. It is an important area of research. There is this opportunity for you on the commission to say something about this area and we will take Alex's request seriously and provide you some background information that would then help you make some potential recommendations in this area.**

**DR. SHAPIRO: Okay. Thank you very much.**

**We are going to take a very brief break now. I want to start again at 3:00 o'clock to get us back on schedule so you really just have a five or ten minute break.**

**Once again let me thank our guests very much for being here today. Thank you very much.**

**(Whereupon, at 2:54 p.m., a brief break was taken.)**

**DR. SHAPIRO: Colleagues, we have really a very special panel to hear from in just a few moments. That is, as you know, panelists, all of whom, who have participated in research as human subjects. A very, very important perspective for us to have some feel about and I want to express to all three of you the gratitude of the commission for your willingness to come and spend a little time with us this afternoon.**

**It is very important to us and we are very please that you have been generous enough with your time to come and spend a few moments with us.**

**We had hoped, of course, to have four participants this afternoon. One participant, for reasons I am not fully cognizant of but in any case I am sure quite valid reasons, was unable at the last moment to be here.**

**So let me turn once again to Marjorie who will introduce this panel.**

**Marjorie?**

**PANEL II: INDIVIDUALS WHO HAVE PARTICIPATED IN RESEARCH AS SUBJECTS**

**DR. SPEERS: Thank you. Again I would like to extend my welcome to the three of you for joining us here today and just to say to you do not be intimidated by the room, by the panel, by the table structure. Everyone here is very friendly and very eager to hear from you and to hear your perspectives about research and being part of research studies.**

**Our panel is made up of three individuals today. The first is Ms. Timmeca Wilson, who is from Washington, D.C. The second is Mrs. Susan May from Atlanta, Georgia.**

**DR. MESLIN: Hold on one second. I do not think our microphones are working.**

**DR. SHAPIRO: At least for the panelists let's speak up as much as you can for those but, commissions, especially speak up.**

**DR. SPEERS: And the third panelist is Ms. Linda Smith from Perris, California.**

**(Technical difficulties.)**

**(Whereupon, a brief break was taken.)**

**DR. SHAPIRO: Okay. We are going. Colleagues, Bernie, Diane, others, I think we are all set and I would like to get the meeting going again.**

**Again, let me apologize to our guests for the delay. I very much regret that.**

**Marjorie, can we go ahead?**

**DR. SPEERS: Yes. Thank you.**

**We would like to begin by asking each of you to tell us something about yourself. Tell us who you are, the type of research that you have participated in or that you are currently participating in, and why you are participating in the research. We would like to just start by having you make a very brief statement as long as you would like it to be but a brief statement about who you are and why you are in research. And then we will have some general discussion.**

**Timmeca, would you like to go first?**

**TIMMECA WILSON**

**WASHINGTON, D.C.**

**MS. WILSON: My name is Timmeca Wilson. I am 21 years old. I am a participant of the REACH program. I am also on their committee advisory board. I have been a member for five years and the reason why I decided to join the program is because I thought it was important that, you know, just through adolescence that they are trying to find a cure for AIDS and HIV, and that they use us as, you know, the door in to finding that method. So that is the reason why I joined.**

**DR. SPEERS: Can you tell us what REACH stands for and the kinds of things that you do in your research study?**

**MS. WILSON: Yes. REACH stands for Reaching for Excellence in Adolescence Care and Health. And what was the other question?**

**DR. SPEERS: What are the kinds of things that you do in your research study?**

**MS. WILSON: Well, they have two sides to the study and that is the positive side and the negative side, and I guess the negative side is somewhat of a control. And what I do as a control is I give blood. I do certain -- they do certain samples and I guess what they do is -- what they do is they compare it to the positive side to see maybe what differs and that -- just in that sense what they can do in order to make maybe the process for people who have HIV and maybe AIDS, how they can help them with medicines and curing their diseases.**

**DR. SHAPIRO: So is it the case that the type of intervention which you have experienced is limited to blood draws over time and perhaps attending meetings and other things of that nature? I am just interested in what you have to do as a participant in this project.**

**MS. WILSON: Well, it is very much more than that depending on what role you take. As me being on**

**a community advisory board I try to get to other participants to get them to speak to me so when I go to annual meetings I can give feedback to what their concerns are and, you know, during the program there was concerns about the blood, how much blood they took, some of the -- well, let me see, how should I say this?**

**Some of the tests, you know, were uncomfortable and they brought that to the attention -- to my attention so that I can bring it to their attention to see if they change the way that they do that particular study so it would not be so uncomfortable.**

**Other than that I have not -- just by myself being a participant and me being on a committee, the community advisory board, I mean, everything else seems to fall into place and if there was a problem I am pretty sure just by me being a participant that I would feel uncomfortable about it also and that I would bring it up in one of the annual meetings.**

**DR. SHAPIRO: Thank you.**

**DR. SPEERS: Thank you.**

**DR. SHAPIRO: Trish, did you want to ask some questions?**

**PROFESSOR BACKLAR: May I?**

**DR. SHAPIRO: Yes.**

**PROFESSOR BACKLAR: Thank you so much, all**

**of you, for coming. I am anxious to hear all your stories. I wonder if you can tell me how did you get involved with this research?**

**MS. WILSON: I was, I guess, about 16, maybe 17 years old at the oldest, and my nurse practitioner that I had been with for about four or five years asked me did I want to be a participant in a program. She felt that I was responsible enough to make the appointments, you know, as being a member of the -- a participant of the program.**

**As me being a minor, I had to make the decision and my parent had to make the decision if they were going to allow me to be a participant in a program so my mom had to sign a form saying, yes, it was okay for me to participate, and I thank her for that because, like I said, it is a really good program and I wish that others would go -- you know, if they had the opportunity would join programs like this.**

**PROFESSOR BACKLAR: Thank you.**

**DR. SHAPIRO: Thank you. Yes, Diane?**

**DR. SCOTT-JONES: You mentioned that your parents signed a consent form for you.**

**MS. WILSON: Yes.**

**DR. SCOTT-JONES: Now that you are an adult do you give consent for yourself? Do you -- are your parents still involved in --**

**MS. WILSON: No. I sign everything, you know, now that I am an adult. I sign everything.**

**DR. SCOTT-JONES: And then do you have interactions with others who are in the study? You mentioned that you talk about some of the things that are going wrong with the others who are in the study. So do you know the other people who are in the study?**

**MS. WILSON: That is not how I get in touch with them. What I usually do is I send out a letter and some people respond anonymously. I do not know any of the participants in persons. So, no.**

**DR. SCOTT-JONES: Thank you.**

**DR. SHAPIRO: Jim?**

**DR. CHILDRESS: Just to follow up, are you able to -- you have said something about your own motivation for participating, do you have some sense about the motivation of other participants, of why they decided to --**

**MS. WILSON: I think it has a lot to do with teenagers today do not have health care and I know that that was one of the reasons why I joined the program is because under the study I was able to be seen by a nurse practitioner or a doctor and it was not like if I got sick I could go in but when I did go in for the study if there was something wrong with me they could check me out at that time, you know, and I would be seen under the study.**

**DR. SHAPIRO: Rhetaugh?**

**DR. DUMAS: Hi.**

**MS. WILSON: Hi.**

**DR. DUMAS: Thanks for coming.**

**MS. WILSON: Thank you for having me.**

**DR. DUMAS: Tell me what do you understand to be the length of time that this study goes on. Is there a limit to the study? Is there a special time boundary for the study to end?**

**MS. WILSON: Well, me being on a community advisory board I know that it does end December the 1st of this year so as far as --**

**DR. DUMAS: And what do you think -- what do you understand will happen at the end of the study?**

**DR. SPEERS: Ms. Wilson is looking at Dr. Audrey Rogers who is the project officer for the REACH project from the National Institute of Child Health and Development at the National Institutes of Health.**

**DR. ROGERS: Right. We are currently composing and will take to our steering committee at their July conference call for their approval a letter of appreciation to each one of our subjects who has participated in the study. Also, findings, the primary findings of the study, particularly those that are specific to their continuing health care, and also a letter that describes -- a FACT sheet that**

**describes to them what our repository is, what the specimens are that are in there, how people access that repository, and get -- and stressing to them their ability, their right to withdraw their permission for specimens in the repository to be used. And that package is going to go out to all subjects in the fall.**

**DR. DUMAS: Then the health care that Ms. Wilson is getting now will terminate at the end of that study?**

**DR. ROGERS: Ms. Wilson is not getting health care within the context of the study. What she is referring to is that there is a screening package for STDs and for other infections that are common in teenagers that is done on a routine basis, and that information is made available to her health care practitioners.**

**DR. DUMAS: But there is no treatment --**

**DR. ROGERS: There is no treatment.**

**DR. DUMAS: -- that is a part of this study.**

**DR. ROGERS: This is a total observational study, biomedical/biobehavioral.**

**DR. DUMAS: But the screening stops also?**

**DR. ROGERS: Yes, ma'am, it does.**

**DR. DUMAS: Thank you.**

**DR. ROGERS: You are welcome.**

**DR. SHAPIRO: Trish, did you have another**

**question because I do want to get on to the other panelists so this will be the last question.**

**PROFESSOR BACKLAR: I just wanted to follow up. I just wanted to thank you again. I just wanted to follow up. You said, if I understood you correctly, that you were interested in coming into the study because of the opportunities for health care and so you -- but you also said when I asked you how you got involved that your nurse practitioner told you about it so you were already receiving health care?**

**MS. WILSON: No, not at the time. I did not have health care. You know, I was not receiving any health benefits at all. I had to pay for those services and through the REACH program I did not have to pay for screening, you know, now that Audrey cleared that up. I did not have to pay for screening. Those tests were done through the program and that was something that I did not have to pay for.**

**PROFESSOR BACKLAR: So that your meeting with the nurse practitioner was something that was not part of your general health care? It came to you in a special kind of package, is that correct, that your involvement with this REACH program before you got into the study? I am sorry. I am a little confused about this.**

**MS. WILSON: Okay. I will just say it. If you do not mind, I will say it again. Before I became a member of the REACH program I was not just able to go to the doctor and not, you know, worry about being -- you know, I had to pay for those types of screening that REACH provided for me. When I became a member of the REACH program since it was through the study I did not have to pay for those type of tests.**

**PROFESSOR BACKLAR: But that was before you enrolled in the study you got --**

**MS. WILSON: Meaning I had to pay for those services. I do not understand the question.**

**PROFESSOR BACKLAR: You understand what I --**

**DR. SHAPIRO: I do understand and my understanding is, I think, as you have described quite clearly, is that --**

**MS. WILSON: Okay.**

**PROFESSOR BACKLAR: Yes. It is not what you were saying --**

**DR. SHAPIRO: She was purchasing these services before joining the study.**

**MS. WILSON: Okay.**

**PROFESSOR CAPRON: She was getting health care on a purchase basis.**

**DR. SHAPIRO: Yes.**

**PROFESSOR BACKLAR: Right, and she had a**

**nurse practitioner that told her about --**

**DR. SHAPIRO: Yes, purchased. She had purchased.**

**PROFESSOR BACKLAR: A purchased nurse practitioner.**

**PROFESSOR CAPRON: She paid --**

**PROFESSOR BACKLAR: I do not know. You see that is what I am trying to find out.**

**DR. SHAPIRO: No, it is paid for. Yes, it is.**

**PROFESSOR CAPRON: She paid.**

**PROFESSOR BACKLAR: All right.**

**DR. SHAPIRO: I do --**

**PROFESSOR CAPRON: One very quick question.**

**DR. SHAPIRO: If it is a very brief question.**

**PROFESSOR CAPRON: It is very brief. It was not clear for me with the comment from Ms. Wilson and from the physician from NIH, is the information that she just described will be sent to the participants a repeat of information that was given to people at the beginning of the study or is it a new statement of what the circumstances are as the study ends?**

**MS. WILSON: Okay. Well -- okay. This is how I can explain it. This is how I am understanding your question. When I go to my REACH visits -- when I go to my REACH visits, every time I see the nurse**

**practitioner who does that study, she does a new evaluation of me so every time it is a new evaluation. So say, for instance, if I came to one study and I had something then, you know, I would find out -- I would find out. But if I did not -- okay. Say, for instance, the first time I had nothing and the second time I went and they did the study and I had something, they would tell me. The next time I go I might not have anything. Is that --**

**PROFESSOR CAPRON: What I was saying was we were just told that a letter is being prepared for the participants to tell them some information about how the study is ending, about what will happen to the data, about their getting access to the data, about other people having access to the data, and I just wanted to know was that something that was said at the beginning and this is just an opportunity to say it again as the study ends or is this a statement which was not fully worked out at the beginning of the study and is being worked out now?**

**MS: WILSON: Do you want to answer that?**

**DR. ROGERS: I think I would like to. We are reiterating in the letter to the subjects some of the information about the privacy and confidentiality of the data in the final letter. There is one piece that was not in their original consent form and that had to do with their right to withdraw their**

**permission for specimens in the repository. Those forms were drafted in 1994 and thinking has evolved on repository rights and permission. So we are clarifying that and making sure they have that information.**

**We also -- in terms of the information we are giving them, it is very specific to findings from the study.**

**DR. SHAPIRO: Thank you. Ms. Wilson, I hope you will remain as we move to other members of the panel.**

**Marjorie?**

**DR. SPEERS: Ms. May, would you like to tell us about yourself and the research you have been in, and why you were in it?**

**SUSAN MAY**

**ATLANTA, GEORGIA**

**MS. MAY: Thank you. Thank you very much and thank you, commissioners, for inviting me to talk about my situation.**

**In August of 1997 I was diagnosed with non-Hodgkins lymphoma and I started the regular treatment for that, which was a series of chemo -- it was chemotherapy called the CHOP program and I improved right away. It never quite did the trick, though, so by the -- early the next year in early '98 I was scheduled for a stem cell transplant, which would**

**allow the doctors to give me high dose chemotherapy.**

**Well, I was very relieved after that to find that the CAT scans showed no signs of the lumps and bumps that I had had before and I still felt pretty punk but it was very optimistic. Unfortunately, in July of that year, however, after a few months of remission, I found a small lump in my neck and went right to the doctor and sure enough there was cancer back and including a mass in my abdomen where the primary site had been originally.**

**At this point it seemed as though it was growing pretty fast. My doctor said that there were still some options open to me, which was a kind of surprise to me because I had thought that stem cell transplant was the big one. And I was very grateful to hear that I could try monoclonal antibodies which had -- were on the open market at that time and were available to be used but my oncologist also said that I was a candidate -- I was eligible to be on a clinical trial, a Phase II clinical trial, for a new immune booster, one of the biologicals called Interleukin 4. And it was for people who had lymphoma and who had flunked stem cell transplants.**

**So at that point my doctor said, "You know, you have a choice here. You could go right to the monoclonal antibodies, which have proven to be effective in some cases of such --" of my kind of**

**lymphoma "-- or you could try this IL-4 on the study. It is your choice but if you choose IL-4 -- if you choose monoclonal antibodies and it does not work you would be ineligible for the IL-4 study."**

**So my husband and I talked it over -- well, we did not even talk really, I guess, that much. We just said, "Well, let's try the IL-4 first and then if that does not work I will have a plan B."**

**But the bigger question is why did I even say yes to a clinical trial at all. I have to tell you that at the beginning of this -- my medical -- my illness, I had come to that with a real prejudice against trials. I think I thought that clinical trials just used you like guinea pigs and that they could harm you or they could not help you necessarily and that it was just definitely a long shot, and I did not really even at that time understand there were Phase I, Phase II and that sort of thing. And the more I learned about it, the more comfortable I felt with the idea of being in a clinical trial.**

**One of the reasons that I also said yes was that I had been attending a support group led by a particularly marvelous facilitator, a woman who was trained as a chaplain but had an unusually broad knowledge of cancer treatments. The support group was for people with all kinds of cancers and so many people in that support group had had positive**

**experience with clinical trials that that gave me a lot of reassurance.**

**Also Betty Castellani, the facilitator of the group, said, "You know, you have tried chemotherapy. That worked just -- it did not do the trick for you. Perhaps it is time to try a different approach," and this immune boosting interleukin was one of those approaches.**

**So I had an attitude of acceptance and trust going into the study and sure enough two months after I started taking these three injections a week my tumors had stopped growing. Two months after that they started to shrink and six months after that there was no sign of any tumors and I was slowly starting to get my energy back. And I was just incredibly grateful for that.**

**In the mean time I continued to take the injections and did so for what turned out to be about 14 months. I must admit, though, I was a little bit shocked when Dr. Moore called me in last September and said, "I would like to report to you that you will be ending your time with Interleukin now." And I said, "Oh," because I felt as though that had given me the boost I needed to stay well. And he said, "Well, as it happens, the manufacturer will not be making this any more because of the 50 of you on the trial, only two of you benefitted."**

**And knowing how near death I was in August of '98 -- I mean, I -- I know those other 48 just did not make it. And so it was very sobering and sure enough I stopped taking the injections but by last December all of a sudden this kind of veil lifted and I really felt great. I was back to being my old self and I am in remission today, feel great, and I believe we will never know whether IL-4 did it for me.**

**But whether it was just plain dumb luck or this wonderful immune booster that I needed, we will never know but I know that I was very grateful to have had some options at that point.**

**DR. SHAPIRO: Thank you very much. Let me see if there are any initial questions for Ms. May about this. Alex?**

**PROFESSOR CAPRON: Was the Phase II trial that you described one in which you as an individual were getting graduated doses to explore the tolerable level and the metabolic response or were different subjects getting different doses?**

**MS. MAY: No. As far as I know, this was out of the University of Arizona by the way. No. I believe that everyone got a dose but it was calibrated to your weight. As I slowly gained a little weight after being anorexic there for a while.**

**PROFESSOR CAPRON: Could you describe for us**

**-- one of the -- obviously the great values of hearing from subjects in research is helping us to understand how the research process is presented to and perceived by subjects and could you explain what you think the different phases as you became aware of them from the research or from the support group you were in, the different phases of research do. And particularly obviously a concern is if at various points in research placebos are used or an alternative treatment to the one that is actually being studied, what -- how that puts in perspective what the goal of the research is and the possibility of benefit to the subjects?**

**MS. MAY: I understand that in Phase I that there are blind studies done. There are some who get placebos and some who get treatment. That may or may not be right but that is just my idea of it. I know this was a Phase II study and I was assured that I was actually getting the medication.**

**I think -- Marjorie asked me to answer this question, too, about whether I felt like a subject or a patient. And I must say I was most -- I mostly felt like a patient that just out of the blue, came a treatment that I had never heard of and that was available to me.**

**My doctor happens to be very calm, he does not talk a lot. I got the rest of it from my support**

**group. But, you know, I did fantasize as a subject, though, that I was part of this pioneering effort that was going to change things for people with lymphoma and that made me feel great. I was stricken when I heard so many other people did not make it.**

**DR. SHAPIRO: Laurie?**

**MS. FLYNN: Thank you very much for sharing. Really it is a wonderful story. I just have one additional question. You indicated how wonderful it was that you were one of only two who you surmise may have benefitted. What kind of information was shared with you? How was it shared about the potential positive outcome or the potential for a not so positive outcome? What were you told?**

**MS. MAY: I was told nothing.**

**MS. FLYNN: You just went into this with a sense that nobody knew anything and you would be part of the learning?**

**MS. MAY: That is right. I was very sick. You do not even think about things like that when you are so sick.**

**MS. FLYNN: I understand.**

**MS. MAY: You know, I just -- I had -- by this time I had so much trust in my doctor and in my support group and I mean it -- I just was there. In the earliest stages my husband had done tons of research. He works for CDC. He had doctors and**

**everybody looking -- I let him do all that but in this case we just rolled with it. We were told nothing and I still do not -- all I know about that study is that 48 of the people did not make it. And I know that Dr. Moore said that they are writing up the study and that that will be out at some future date.**

**MS. FLYNN: Thank you.**

**DR. SHAPIRO: Diane, do you have a question?**

**DR. SCOTT-JONES: I have a question about what you would say to others who are considering whether to participate in a study given your wonderful outcome but the not so wonderful outcome for the majority of people who were in the study? What would you say to someone who sought your advice?**

**MS. MAY: You make the best decision you can at the time and I believe I understand intellectually that even negative results are, in fact, results that are information that can then help researchers build on the next steps.**

**But I will tell you there were times when I thought, you know, if this does not work have I waited too long to try monoclonal antibodies? Some of these biologicals work so much slower on your body than does chemo which just blasts you immediately with treatment and so that just was a chance I decided to take. I knew I could stop any day I**

**wanted to. That was another thing that I felt very -- a lot of trust in with my doctors. I never felt coerced. I just felt -- I felt that I had got good information. It happened my doctor was -- and I chose him for this -- was head of clinical trials for DeKalb medical center. And I knew that -- I knew that he had saved the lives of two of my best friends so I knew he was very, very good.**

**DR. SHAPIRO: Thank you.**

**Larry, then Arturo, then Trish.**

**DR. MIIKE: Ms. May --**

**DR. SHAPIRO: Sorry. Did I interrupt? You had another question, Diane. I apologize.**

**DR. SCOTT-JONES: You mentioned that when you were deciding whether to be in the study you were very sick and you sought your doctor's advice and also you said your husband did a great deal to gather information for you. How much did you consult with your husband or other family members when you were making your decision whether to be in the study?**

**MS. MAY: It was only with him and with the doctor.**

**DR. SCOTT-JONES: Thank you.**

**DR. SHAPIRO: Larry?**

**DR. MIIKE: It is a question related to that. When your initial treatment failed and you were looking for other treatments you had mentioned**

**the possibility of monoclonal antibodies and then it was mentioned that there was this experimental therapy going on. What kind of information was given to you in terms of the success rates of monoclonal antibodies versus the chances of finding something comparable to that in an unproven therapy?**

**It sounds to me like you had considered that but because of trust or some other reason decided to go into the experimental therapy where the information was unknown, where there was some information on monoclonal antibodies. So I would be interested in sort of summarizing your thought process on trying to balance those two issues in the decision that you made.**

**MS. MAY: You know, I do not even remember whether Dr. Moore said anything about my chances with monoclonal antibodies. I just remember that all during my illness I had in my purse this article I had ripped out of a Family Circle magazine that I had picked up in one of the many waiting rooms I had been in over those months. It was about -- showed a woman about my age going kayaking off Seattle and she had been treated for lymphoma by monoclonal antibodies and she had survived, and so I just clutched that as a positive. Something positive.**

**But, frankly, I do not remember that Dr. Moore said anything about my chances.**

**DR. MIIKE: Right. So that information was something that you had gotten on your own?**

**MS. MAY: That is what I had gotten. You know, and I read the paper and it is in there. But I think I chose to do IL-4 and to be on this study because that would give me one more option if it did not work. If I had chosen the other way around, I would not have been able to try it. If I had gone to monoclonal antibodies first I would have been ineligible for IL-4. It was strictly having more options.**

**DR. SHAPIRO: Thank you. I have on my list here Arturo, Trish and Steve.**

**DR. BRITO: I had the same question.**

**DR. SHAPIRO: The same question. Trish?**

**PROFESSOR BACKLAR: I wonder if you would be kind enough to engage in a little thought experiment for us. If you had -- if you had been one of the people who had not -- where this -- where this had not worked for you, do you think that you would have looked at your clinician differently? Could you imagine yourself in that situation and how you would be thinking things through? And you have spoken a great deal about how much you trusted your clinician as things turned out for you but if it had been different.**

**MS. MAY: I do not know.**

**PROFESSOR BACKLAR: I am asking --**

**MS. MAY: Yes, I really -- I am actually -- I think it is your personality whether you blame or not. I mean, I think that he gave me plenty of room to just not bother -- not -- to not do that. There was an ease there and if it had not worked we would have known in the two months. You know, you had to wait a couple of months so that you could see whether it was working or not. If at two months there had been no change or my tumors were growing or if during that two months I had started feeling worse we would have stopped it instantly and started the other program.**

**I have no -- so I do not think I could -- I do not think I would have blamed him. Cancer is really vicious.**

**PROFESSOR BACKLAR: I was not asking you to blame but what I am actually wondering then is how much of a factor -- you used the word "trust" a great deal but you were also explaining how you thought this through for yourself and what you weighed and took into account.**

**MS. MAY: Right.**

**PROFESSOR BACKLAR: So I wanted to hear.**

**MS. MAY: Right. His competency was extremely important.**

**DR. SHAPIRO: Steve?**

**MR. HOLTZMAN: I was just going to clarify in connection with Larry's question that the monoclonals in question have been approved or proven for NHL. They have been approved for other kinds of lymphomas so effectively it was a choice between two experimental therapies.**

**DR. SHAPIRO: Thank you.**

**DR. DUMAS: Just one.**

**DR. SHAPIRO: Rhetaugh, the last question. I want to hear from Ms. Smith in a moment.**

**DR. DUMAS: This is just a confirmation. Am I correct in assuming that although you had a great deal of competence in your physician you felt in the final analysis that you made your own decision?**

**MS. MAY: Oh, yes.**

**DR. SHAPIRO: Marjorie, shall we go on to Linda?**

**Ms. Smith, are you --**

**MS. SMITH: Yes.**

**DR. SHAPIRO: Eager to hear from you.**

**LINDA SMITH**

**PERRIS, CALIFORNIA**

**MS. SMITH: Thank you for inviting me.**

**I am currently participating in a human research study sponsored by a pharmaceutical -- first of all, I want to say you guys really impress me. I had no idea what you did and Dr. Shapiro is correct,**

**I feel a lot less -- and I am really interested in what you have to say.**

**I am currently participating in a human research study sponsored by a pharmaceutical company in La Hoya, California, which is directly next to San Diego. It is like Bethesda is to the city.**

**I have an illness called hereditary angioedema. It runs in families. A child has a 50 percent chance of developing this disorder if one of his or her parents has it and blood tests are necessary to confirm a diagnosis.**

**It comes about if you are short of a normal blood protein called C1 inhibitor or it is also called C1 esterase inhibitor. This protein helps to regulate the complement system which is part of the immune system that helps us fight diseases. When present in normal amounts it helps to turn the complement cascade off. If there is not enough C1 inhibitor, a runaway reaction results.**

**The pharmaceutical company -- correction. People like me with this C1 inhibitor deficiency have episodes of swelling, swelling of hands, feet, face, tummy and most threatening, the airways. Swelling of the airways can be deadly and if not treated -- if they are not treated and controlled properly.**

**Attacks may occur without any cause. However, anxiety, stress and minor traumas like**

**dental procedures can trigger episodes. The frequency and the severity of these attacks are unpredictable. Completely unpredictable.**

**The pharmaceutical company sponsoring this study uses C1 inhibitor concentrates made from human blood to determine its effectiveness and safety in relieving these attacks. This is the FDA Phase III. The final stage of this clinical trial, which is used to support application to the FDA for this drug to be licensed in the United States. It is also licensed in a few countries in Europe where there is considerable experience in using this drug to treat attacks of hereditary angioedema.**

**Alternative treatments, other things to use instead of this are in the form of antigens such as danizol, winstrol, oxagelone, which I am taking now, and I have taken winstrol. The side effects to these medications are very undesirable, including masculinization, weight gain, most importantly liver problems. That is very undesirable.**

**As a participant I have been made completely aware of the entire research process by the principal investigator and the entire staff at the Scripps Research Institute in La Hoya where I go whenever I am having an attack. I have been involved in this research study since June of 1997 and I can speak proudly about the excellent treatment that I receive.**

**If you ever want a model study program, go and talk to them.**

**It is -- I -- at one time in 1995 I was asked to participate in another clinical study regarding another misdiagnosis of my condition and one of many in my history. This particular time physicians at Loma Linda University medical center requested that I participate in a study to determine that I suffered from an autoimmune disorder.**

**Well, I was having an attack as I do with my stomach pains but as I told you they are unpredictable. I have had three throat attacks and I swell all the time. I was admitted to the hospital under their specific protocol and this was the first and the only time that I went there for treatment.**

**I was treated with complete neglect. I was not informed or guided by anyone. I was not instructed anything. Not even the nurses would treat me with any kind of special attention. And, in addition and most importantly, the pain was never alleviated. So they were out.**

**At Scripps with regard to consent forms, I sign two consent forms before each treatment. I am with professional doctors and nurses who are familiar with my symptoms and who treat me with respect and compassion. Something that is not -- compassion -- and humility is not one of the favored personality**

**traits of doctors.**

**This here -- my doctor with regard to this study is compassion. I have here a copy of the human consent form and I also have a copy of the experimental subjects bill of rights, which I sign every single time I go down and get an infusion, and I also sign another form for the hospital. So I am -- this is several pages long and it is -- you know, it is all right there and I am treated as a team member in this entire study.**

**I am in the driver's seat. They share everything with me. We talk and discuss everything and I question anything all the time.**

**I have been mistreated and misdiagnosed for more than 20 years. After so many years of seeking doctor after doctor who would listen to me and believe me, since I always swelled my mother is who I inherited it from. One time in 1984 when I was preparing for some major dental work, a dental procedure, I mentioned to the technician that I often swell when I do dental work, and she said, with all knowledge, she said, "Oh, that is hereditary angioedema." Well, at that time I immediately asked her to show me some literature on this and so she did, and I photocopied it, and I read it, and that is when I knew that my swelling was hereditary angioedema. That is what my mother had and that is**

**what I had and so I was -- I basically diagnosed myself.**

**Then I followed with a laboratory blood test because it said in there that is how and I found an allergist and I said, "Do this test for this," and he did, and then I was confirmed that I had a deficiency in the C1 inhibitor.**

**So I knew that I had that and that was the answer to my swelling but I still did not know what was the answer to my stomach pains and I was proceeding with doctor after doctor, gastroenterologists, gynecologists. "What is with the stomach pain? What is --" It always seemed to come when I had my period and when I ovulated so it always -- that was a trigger. It seemed to be a trigger.**

**So nobody could find anything. Oh, go see this gastroenterologist. Okay. Prednisone, all this, spastic colon, I mean you name it, you know. Had incorrectly -- I was -- had a laparotomy surgery because the stomach pains present abdominal and doctors go in and want to perform surgery. And, of course, once they get in there all they see is swelling and that is -- you know, and it is just not correct. And I am frustrated and I am -- by the grace of God I am not medically indigent so if -- doctors, in my opinion, come a dime a dozen.**

**If you are not there with me then the next one and I would go and I ask and I do that because I have to -- I am my own best doctor. In my personal belief, I am alone, I have no family, so I have to do that.**

**So after she showed me the literature I followed up again. I still continued to seek diagnosis for my stomach pains. Well, I was in a very severe automobile accident in 1984 and I was in a coma and from that I received traumatic arthritis so I was -- one day I went to consult with my rheumatologist because I was having pains or whatever, you know the routine.**

**So I mentioned to him that I had hereditary angioedema just in talking because he is another compassionate nice doctor. And I told him I had hereditary -- and I could not understand that I always had these stomach pains when I swelled.**

**Well, because I said that, this man is a forward thinking man, he said, "Okay, this is what I want you to do. Call this Dr. Simon at Scripps University in San Diego." He said -- I am sorry. I am nine minutes.**

**DR. SHAPIRO: That is all right. Do not rush.**

**MS. SMITH: He said, "Tell him. Call this guy and tell him that you have hereditary angioedema**

**and he does not know about you." So I did that immediately as soon as I got home. This was how I first learned about the study of which I am now enrolled. I have never been happier.**

**As an example of medical doctors who refused to be forward thinking, this is an example of one of those unhumiliated doctors, I became enrolled in this study and I interviewed them. I mean, I talked to Dr. Zure and all the people and I asked question after question after question. He gave me something like 20 something pages of information and I always -- I can call them right now on the phone. I mean, it is -- they are right there with me.**

**I copied -- I photocopied all this stuff and I went to this gastroenterologist that I was seeing and I had went to him because I wanted to give him this evidence in case there are other people like myself who come in there with the same symptoms that he -- I gave the phone numbers to these doctors to call the Scripps, and da, da, da. And you know what he said to me? He turned around and said to me that I was wrong, all of my research was wrong, it was not true, and he was rude, and I said, "Thank you very much." Needless to say I do not see him and I specifically spoke to the doctor who referred me to him and said something to him about that. So that is that story.**

**The other thing is -- that is important is I work for the Federal Aviation Administration right here across from the Aviation Smithsonian, 500 -- what -- 5000 Independence Avenue or something. I provide air traffic services as an occupation. I am also a commercially licensed instrument rated pilot.**

**My job requires very strict medical guidelines to be followed so as not to jeopardize safety as you all, I am sure, well know. Any drug that can slightly affect our decision making in any aviation instruction is completely forbidden obviously.**

**I am restricted from performing my duties if I would have -- if I would have to take the medication demerol, which coincidentally happens to be the only drug that alleviates stomach pain. For example, as we speak now, I am not having an attack but, you know, I could because of the stress. But if I did I could not get treated here in Washington. Unfortunately, there are not any places. But I would have to go to the emergency room, of which I have a doctor -- a letter from my doctor explaining my condition and what -- to give me demerol and keep me -- because I dehydrate so to keep me moistened up.**

**So I would take demerol. Therefore, it would be very important -- where am I? I am sorry. So I am restricted from performing my duties if I**

**have to take demerol medication until that drug is out of my system.**

**So, therefore, it is very important for me to proceed to the Scripps hospital immediately when I feel the onset of an attack because it takes me two hours to drive to Scripps clinic. If my attack progresses at a rapid rate because we know that it is unpredictable and the severity is unpredictable, sometimes it proceeds really fast and sometimes it is slow. If it goes really fast and I am in a lot of pain, which I normally do as I always think, oh, maybe it will go ahead, maybe it is not an attack, and then I do not start leaving until when it is late and then I forget that two hours down the road I am going to be worse.**

**So at that point -- now at that point -- duh -- I might need to use demerol for the pain and then I am restricted to go back to work until the drug is totally out of my system.**

**These are just the things that I have to work with and I am much more thankful that I have a place to go now. I have a place to go now with people that know about my condition so I am much more thankful for that and I just need to adjust my times to go down and get going.**

**I have been -- that is it for that and let's see -- oh, my gosh, it is 12 minutes now. There is**

only two more quick things and -- quick and important things that in my opinion -- first of all, and I am going to say this twice, we have a website, a patient advocacy group and we have a website. It is www.hereditaryangioedema.com. Last year in 1999 the National Organization of Research -- I mean, of Rare Disorders had their conference here in the city.

A segment of the program was dedicated specifically towards people living with what I have, my illness, hereditary angioedema. One of the agenda items was in developing an organization of patients, a patient advocacy group. Eventually, you know, we -- patients have a lot of input. Well, so there was in March of -- in March of this past year, '99, two people started an open forum web page to communicate with others who suffer from this illness. As of the 10th of July there are 197 people on that list.

This web page offers emotional support, education, evidence, first person accounts of treatment and mistreatment. We have united and we aspire to change our future.

The last item is that the specific pharmaceutical company that is sponsoring this requires 150 people -- and I am a member of 15 that are Scripps. I do not know what the total is that are already participating or how they will reach that, and then apply for application with the FDA.

**But the physicians, they have a protocol and there is many hoops that physicians have to be extremely dedicated together and they have to have a strong interest in this to participate.**

**So it is hard to get -- to urge physicians to get one of these studies going so that is one of our problems or our challenges, you know, to get more people because we get on the website people that are suffering all the time with doctors that, you know, do not believe us and so there you go. It is 13 minutes about. I am sorry.**

**DR. SHAPIRO: Please do not apologize. Thank you very much.**

**MS. SMITH: Thank you.**

**DR. SHAPIRO: You are very, very informative. Let me see what questions commissioners have.**

**Rhetaugh, do you have a question?**

**DR. DUMAS: Yes. Thank you. That is a remarkable story.**

**What is going to happen to you when the project is terminated?**

**MS. SMITH: Hopefully, the FDA will approve it.**

**DR. DUMAS: And?**

**MS. SMITH: And then this particular drug -- pharmaceutical company will have the option to**

**produce this and there is going to be a challenge to convince insurance companies to cover it. It is supposedly -- rumor has it that it is a lot of money and they could price themselves out of business. We would have to resort to antigens. Myself before -- I am taking the antigens now but I do not like to take pills and before that when I -- the last thing I want to do is deal with an emergency room. And I would be mistreated there and I would just stay at home and suffer. I mean, it lasts about -- the hardest -- the strongest part of the pain is initially 24 to 36 hours and then it starts to wane off. It is like -- it swells your intestines up and creates a real severe chronic pain that comes in waves and it is --**

**DR. DUMAS: You apparently have a very good relationship with the people at Scripps.**

**MS. SMITH: I am lucky.**

**DR. DUMAS: Now what is going to happen to that relationship? Is that something that has been negotiated? Have you discussed that? Will your relationship with Scripps terminate when the project terminates?**

**MS. SMITH: Sure. Certainly. I will always have them to talk to. They will always be there to talk to no matter what and they will refer me because they are -- you know, they are doctors and they will refer me and help me and, you know, they will**

**prescribe me antigens.**

**DR. DUMAS: They have said they will always be there to talk to you?**

**MS. SMITH: Oh, yes. Yes.**

**DR. DUMAS: Thank you.**

**MS. SMITH: Thank you.**

**DR. SHAPIRO: Thank you. Other questions? Any other questions from commissioners for any of our three panelists? The stories together really tell us quite a lot.**

**Larry?**

**DISCUSSION WITH COMMISSIONERS**

**DR. MIIKE: I just want to ask, Ms. Wilson, what is your understanding -- you talked about there is a positive arm and a negative arm and you are in a control group. What is your understanding of the purpose of the research? What are they trying to determine?**

**MS. WILSON: Well, when I became a member and just by being on CAB -- let me see how I should say this. I think even though they might have told me what the purpose of the program was when I joined the program, I made my -- I kind of like in my own mind made my own purpose and that purpose was to find a cure through adolescents for HIV/AIDS and that is just how I thought about it for the five years I have been in the program.**

**DR. SHAPIRO: Thank you.**

**Alex?**

**PROFESSOR CAPRON: I have a sort of combined question for Ms. Smith. The quality of the care that you are receiving at Scripps is obviously very good and it would be my impression from what you have said about the nature of your condition that most treatments for it would be in a research context still almost anywhere you would get treatment. And so the contrast is between an institution that does a very good job of attending to the patient side of the research and ones which you have described that do not do a good job and physicians who outside the research context apparently have not done a good job. Is that a correct description and, if so, is your participation in research really a result now of that quality of the doctors as the researchers as doctors? Is that a fair statement?**

**MS. SMITH: Certainly. There -- definitely because I go by feel. I mean, you know, if they did not come across as professional -- and they told me over and over again it was, you know, research and everything, and I -- and at the point where I was, I mean I had been everywhere. Sure, I will give it a try and if I do not like it or I do not like you or something I will not come back. I can suffer. I mean, I can suffer with it if I have to but I will**

**not be mistreated. So, yes, definitely.**

**I am lucky because I just told you there was another study that I was in that was -- and I never went back there. They could not help me. I am -- you know, we need to work together on this.**

**PROFESSOR CAPRON: You seem to be active in the group of people who -- several hundred people in the country perhaps who have -- are you aware of other people's stories?**

**MS. SMITH: Yes. I listen -- the website is open. As a member there is an open forum. Like if you went to look at it you would not be able to able to go into the website, the open forum, but everybody -- I do not respond much. I talk to a few people on there but if you know -- those of you that are doctors know that sometimes people can, you know, over dramatize everything and then sometimes people who are ill want to be ill in so many ways and they want to take all kinds of drugs and be sick, sick, sick, and want help and there is -- you know, but -- so I do not -- I mean, I -- there is lots of e-mails that I do not even pay attention to. But some of the stories are -- I generally scan through them and some of the stories are very interesting.**

**PROFESSOR CAPRON: The reason I was asking was I wonder whether it would be true to say that the people who are seeking participation in research on**

**this disease are doing it because they see it as their major or only real way of getting appropriate medical interventions for their condition?**

**MS. SMITH: Yes, definitely. Definitely.**

**PROFESSOR CAPRON: Thank you.**

**DR. SHAPIRO: Arturo, and then we are going to -- I have a comment and then we are going to conclude with Marjorie.**

**DR. BRITO: Thanks once again, all the panelists. It has been very informative.**

**Ms. Smith, one thing, once you were diagnosed with hereditary angioedema and you mentioned that you were under some medication, what I am curious about is when you entered the research protocol what was your understanding of the risks involved in trying the new medication and the likelihood that it was going to be a superior management than what you were taking before that?**

**MS. SMITH: I read the Merck or the PDR. I read the PDR, the Merck. I mean, I check that stuff myself no matter what I take.**

**DR. BRITO: No, I understand that.**

**MS. SMITH: Okay.**

**DR. BRITO: Okay. So what was your understanding from reading the PDR and from what was explained to you of the likelihood that it was going to be superior?**

**MS. SMITH: That what I take from them, the --**

**DR. BRITO: From the research, right, as opposed to what you were on before.**

**MS. SMITH: Oh, because it is -- what I miss. It is taken from human blood. It is the C1 esterase that replaces it. It was worth a try. There was -- I could have said no and I can always say no. It was definitely worth a try.**

**DR. BRITO: Okay. Worth a try. I would like to hear a little bit more about what you were feeling like before you started the research and what the problems were with the other medication that you were under that you were personally having with them. It just was not controlling it?**

**MS. SMITH: I was not -- no, I was not having any medication with them. I am taking oxedran now because it is an antigen and because I have -- at this time I have attacks about every other week. I have attacks quite often. And people go in phases.**

**I mean, sometimes they can have -- at one time back before 1995 I had attacks one to three times a year. Now I have them one to three times a month and I have to drive down there two hours and so in order -- that is management to take the antigens at the lowest dosage. And oxedran has no side**

**effects and it is pretty much a new drug and it has no side effects so that is why. The winstrol makes you not have your period and then, you know, there is other things like that. Going to see -- but I am taking that to hopefully -- it affects the cascade somehow that it may reduce the amount of attacks. It will not completely omit them but it will reduce the amount of attacks.**

**So if I have attacks once a month as opposed to three times a month that would work. So I take -- you know, I take two a week or three a week and I -- that is how you do it is you take it enough to adjust it to that breakthrough but I did not take that stuff before I saw him. I was taking -- I was not taking any medication. So I wanted to do it because I did not want the pain anymore.**

**DR. SHAPIRO: Well, if you will tolerate really a side comment that somewhere in your story there is a rather wonderful dental technician.**

**(Laughter.)**

**MS. SMITH: She is.**

**DR. SHAPIRO: She ought to be brought to some place and ensconced --**

**MS. SMITH: Yes, exactly. I even have a copy of that original article. Yes, she is.**

**DR. SHAPIRO: Marjorie?**

**DR. SPEERS: I have a question that I would**

like to ask the three of you. In the research world we refer to people who participate in research as human subjects. And some people like to use that term because it conveys the relationship between the researcher and the person who is participating in the research.

Others do not like the term human subject and have suggested that other terms be used like "participant" or "volunteer."

And I wanted to ask the three of you who have participated in research how you would like to be referred to by researchers and by all of us who talk about people who participate in research.

MS. WILSON: Yes. I would rather not be called a human subject. Participant or volunteer is fine. I feel like people who participate in REACH studies, we give our time, you know, and there is not many people who are willing to give an hour or two or however long it takes out of that day or how many other days it takes to do a study, you know, so I think that -- I mean, whereas that sounds very -- that does not sound nice at all and I think volunteer or participant is nicer. It is a nicer term.

DR. SHAPIRO: Ms. May?

MS. MAY: Yes. I agree. I would actually lean towards participant because to me that conveys a partnership or that you are part of a larger group

**and not just on your own.**

**DR. SHAPIRO: Ms. Smith, do you have a view of this?**

**MS. SMITH: I could care less. I know who I am.**

**DR. SHAPIRO: Okay. Well, once again, in bringing this session to a close, I want to express on behalf of the commission our gratitude to all three of you for taking your time to be here today. It has been very informative and helpful to us so thank you very, very much for coming.**

**(Applause.)**

**PANEL III: VULNERABLE POPULATIONS**

**DR. SHAPIRO: We are running, as is usual, a little bit late so I want to go directly to our next topic here, which has to do with vulnerability of research subjects, a commissioned paper by Professor Kipnis, who did it for us, and I will just allow a few moments for the logistics to straighten themselves up at the other end and turn to Marjorie once again.**

**Is all the technology working? I see.**

**Well, Professor Kipnis, on behalf of the commission once again, I, first of all, want to thank you for the paper that you provided us. I found it very helpful and, indeed, very insightful on some points and really am very grateful for the time you**

are taking to be here with us today.

It is a long way from where you usually work, geographically a long way, and I very much appreciate your effort at being here. So I think everyone has seen a copy of the paper and I would just turn to you to make whatever presentation you think is desirable.

**KENNETH KIPNIS, Ph.D.**

**PROFESSOR OF PHILOSOPHY**

**UNIVERSITY OF HAWAII AT MANOA**

**PROFESSOR KIPNIS:** I will try to hit the high points. First of all, I would like to thank the commission for inviting me out here. It is a pleasure to talk with you.

(Slide.)

The term "vulnerability' seems to have been grandfathered into the discussion of human research subjects without going through anything like the normal certification process.

(Slide.)

As early as the -- in the Nuremburg Code it basically spells it out that informed consent of a subject is an absolute requirement. Right away in writings by people like Paul Ramsey it became clear that we were excluding children and the mentally ill.

And in the early history of -- in the current history of the ethics of human research in

**the United States, three events, it seems to me, stand really quite tall. One is Willowbrook, which involved mentally retarded children who were institutionalized. The second one is the Brooklyn Jewish Chronic Disease hospital case, which is well reviewed in Jay Katz's book on human experimentation. And then, of course -- of course, that one dealt with the infirmed elderly. And then finally the Tuskegee Syphilis study which dealt with poorly educated, impoverished Black Alabama males.**

**Now in all three of these areas, notwithstanding the special circumstances of these populations --**

**(Slide.)**

**-- I think in the minds of many researchers the paradigmatic research subject represents a mature, respectable, moderately well educated, clear thinking, literate, self-supporting citizen in good standing. A man, and I mean that intentionally, who would have no trouble understanding a 12 page consent form and acting intelligently on the basis of its contents.**

**But notwithstanding that paradigm case --**

**(Slide.)**

**-- the current approach does make reference to what I call vulnerable subpopulations. It is what I would like to call a subpopulation focus. That is**

**instead of dealing with the concept of vulnerability, it picks out particular populations for special treatment and the ones I have listed here include children, the ACRE study. The study on the human radiation experiments focuses on the military, and I think it is a very good analysis of forms that vulnerability takes within military research. The mentally ill and, of course, prisoners are not listed there but I do not intend this to be a complete list.**

**(Slide.)**

**The problems that this approach generates really initially is who counts, what populations count, okay, as a vulnerable subpopulation? How do you get to be on this favored list? Okay. Do we include, for example, women who are miscarrying? Do we include the impoverished homeless? Do we include the desperately ill? Do we include Ugandan women? For example, this morning we were talking about women in Uganda. Do they belong on the list or not?**

**And the analytical questions that pop out and that popped out for me and got me thinking about this, okay, is what are the common -- what is the common characteristic or what are the common characteristics that characterize a population as being vulnerable? Secondly, why do these characteristics imply vulnerability? Okay.**

**And, third, this is the most important one,**

**assuming we have a vulnerable subpopulation, what do we do about it? Okay. How do we respond to it?**

**And that is basically what I am endeavoring to answer in this particular paper. And what it does -- let me just say one more thing. What it does -- and I think this is a useful way of doing it. Up to now what we have is this subpopulation approach and there are not very many of them and I think it is an inadequate list. Okay. What I am endeavoring to do is to cut the pie in exactly a different way to look at those characteristics of populations that make us think that these populations are indeed vulnerable vis-a-vis research and so I am really taking a rather different look of the whole -- at the whole area.**

**I think it is one of the things -- I mean, having come at this through philosophy, one of the advantages, I think, I have is basically perhaps being able to look at this in kind of a fresh way.**

**(Slide.)**

**What is vulnerability? This is what I am doing. What circumstances signal it? And what steps should be taken when each circumstance is encountered?**

**Essentially what I will be doing in this essay is mapping conceptual geography. My roots are really in analytical philosophy, ordinary language philosophy, and here some of that is coming out.**

**(Slide.)**

**My other background, by the way, is philosophy of law. I am not a lawyer but I do a lot of work in philosophy of law. This really goes to work that I did several years ago on consent. I think it is useful to see consent as an ethical power. If you ask me, "Can I use your lawn mower, Professor Kipnis?", and I say, "You can use my lawn mower," okay, in saying, "You can use my lawn mower," I bring it about that you can use my lawn mower, something which was not permitted. Okay. Simply in virtue of my pronouncing these words suddenly it becomes permitted. Okay.**

**Now to be sure there are misfires. Okay. If I say, "You can use his lawn mower," you are not going to have permission to use is lawn mower. If I say, "You can kill me," even though I have given you consent to killing me, you are not going to have permission to kill me. Okay. So we need to be aware that there are misfires in consent.**

**So what I have in mind here is that by vulnerability I am really talking about a condition of a candidate subject that calls into question the efficacy of consent in effecting the permissibility of research. Okay.**

**In a case of rape, for example, rape is a really serious crime but only when it is sexual**

**intercourse absent consent. If consent is there, no crime at all. If consent is not there, really, really serious crime. Consent is a remarkably powerful tool that we, I think, take for granted that we can effect certain significant changes in the context that surround us, the systems of permissions and obligations that surround us.**

**I am assuming here that when we talk about vulnerability of research subjects all the usual protective steps have been taken.**

**(Slide.)**

**What we have -- and these are the three elements that I would ask you to think about. First of all, we have a contextually appropriate utterance. Somebody is giving consent under circumstances where it is likely to be assumed to be a granting of permission.**

**Number two, we have its characteristic effect on an action's ethical permissibility. And what it means in the context of research is absent consent of the right sort it is not permissible to conduct the research.**

**And then lastly there are circumstances that can impair that connection. Let me just -- what I would want to say here -- I am not sure -- I do not think I can aim from this far. Okay. Is that showing up on the --**

**DR. MESLIN: Would you like someone to aim it for you?**

**PROFESSOR KIPNIS: Okay. What I have in mind is that the conversation about vulnerability really impairs the connection between one and two. Okay.**

**(Slide.)**

**In talking about vulnerability in general we are really thinking in terms of two things. Okay. First of all, it is a precariousness and there are a certain kind of precariousness in the state of the subject, a state of being laid open or especially exposed to something injurious, undesirable. We can think of a vulnerability as an avenue of attack.**

**And, secondly, whenever we think of vulnerability we are automatically thinking of those others out there who are disposed to capitalize on this weakness, exploiting avenues of attack, intentionally or not to take unfair advantage to the subject's detriment.**

**Now I want to underline that not all vulnerabilities expose research subjects to exploitation by researchers. Okay. A person can be blind, for example, and if somebody is blind they are vulnerable. You can sneak up on them without their knowing about it but that blindness does not necessarily expose this individual to being exploited**

**or treated unfairly by a research subject. Research subjects do not hang around waiting to sneak up on people.**

**And so it is a mistake -- and this is one of the mistakes, I think, in the Common Rule that vulnerabilities are kind of -- that handicaps are kind of mentioned as vulnerabilities when they may not be. The only ones we are really concerned about are those that call into question the efficacy of consent.**

**(Slide.)**

**There are, as of yesterday, five types of vulnerability that I would like to talk about. This morning maybe a sixth one appeared but I will let you guys decide. What I list in the paper are first of all cognitive limitations. I am going to mention them here and I am going to explain them in just a moment.**

**Second, juridic subordination.**

**Third, patterns of deference.**

**Fourth, medical exigency. And that is actually the one that two of these three research subjects were talking about just a few moments ago.**

**And lastly, allocational disadvantage. And I apologize for these five mouthfuls. Okay. But it is the best I am able to do under the present constraints.**

**(Slide.)**

**Here are five questions, each of which point in the direction of the particular type of vulnerability that we are talking about. And I think it is better explained in this slide than it is in the paper.**

**With respect to cognitive limitations the question we ask is does the candidate subject have the capacity to deliberate about and decide whether or not to participate in the study? I will say more about each of these in a moment but I wanted to get them all up on the board.**

**Number two: Juridic subordination. Does the candidate -- is the candidate subject liable to the authority of others who may have an independent interest in that participation? Here I am thinking about prisoners. I am thinking about members of the military. I am thinking about psychology students. Okay. We are basically looking at an institutional structure where somebody is hierarchically subordinated to another individual.**

**Number three: Here we are talking about patterns of deference. Is the candidate subject given to patterns of deferential behavior that may mask an underlying unwillingness to participate? Now in this morning's discussion of undue influence and coercion it seems to me both of these were conflated**

**and they are really quite different.**

**In the first, we are looking at a social structure, a hierarchical social structure. In the second we are looking at a psychosocial response, a pattern on the part -- because I may be deferential even when somebody does not have authority over me and there are people who have authority over me that I am not deferential toward at all. So these are really separate kinds of things.**

**Fourth: Medical exigency, and I will probably say more about this since it really comes up in a striking way. Does the candidate subject have a serious health related condition for which there are no satisfactory remedies?**

**And the fifth one is allocational disadvantage. It is very similar in some ways to medical exigency. Is the candidate subject seriously lacking in important social goods that will be provided as a consequence of participation in research?**

**Now you can look at that last one in a somewhat different way. Sometimes people are not lacking in important social goods. They are rather burdened by social evils.**

**For example, people in prisons -- it is not just that they lack goods. Okay. There is an imposition of unpleasantness upon them that is --**

**that counts as punishment. So we can ask the same question, is the candidate subject burdened by social evils that will be relieved or removed as a consequence of participation in the research?**

**(Slide.)**

**What is the utility of this analysis? Well, one good reason for having an analytic approach to vulnerability is it will provide us with a checklist of circumstances that along with other conditions can invalidate the permissibility of research and as a second reason as well, it is not up there, it will provide us with criteria for designating vulnerable subpopulations.**

**(Slide.)**

**This you all know and we have been talking about it all day and basically research provides benefits as well as risks. Historically I think we have been more attuned to the risks but it is pretty clear especially when you are dealing with medical exigency that for some people it may be their last hope of actually receiving some relief from an illness that is untreatable and then, of course, for populations generically it may be the major way in which advances can be made helping whole groups of people who suffer from particular ailment.**

**(Slide.)**

**In the discussion that follows I want to**

**underline that vulnerability is conceived not as a flashing red light ordering researchers to stop but rather as a cautionary signal calling for appropriate safeguards.**

**If a candidate subject is vulnerable in one of these five ways, the researcher must conduct further inquiry and may need to take compensating steps in the design of the protocol as a condition for proceeding. So that is the model I want to put forward.**

**So let's go now to the first type of vulnerability and what I have tried to do in each of these cases is to lay out the question that directs us towards the vulnerability and then look at the kind of inquiry that ought to be made within that context.**

**(Slide.)**

**Does the candidate subject -- this is cognitive limitations. Does the candidate subject have the capacity to deliberate about and decide whether or not to participate in the study? And here, of course, we are confronted with poor education, immaturity, dementia, mental retardation, mental illness. But I would also want to include other things here that are not usually included under this heading.**

**Several years ago I had occasion to**

**interview women who were research subjects in a clinical trial of tocolytics as a way of addressing the needs of women who were -- well, either in premature labor or in the process of miscarrying depending upon how you reviewed it.**

**They were brought into the hospital in the process of miscarrying and offered an opportunity to participate in a clinical trial of -- I believe it was ritodrine and terbutalene at the time. Okay. And it was quite clear that women who were in the process of miscarrying are not in what early childhood educators a teachable moment. That is the first thing. And, secondly, even if they were the time did not exist to allow them to review all the materials they had to review and to deliberate about it.**

**So even though I would not want to say that women in that situation are demented, retarded or any of those things, I would want to say for a different set of reasons there are cognitive limitations that represented disparity between what it is you need to do cognitively and the resources that are available for really going through the appropriate consent process so I want to include other groups in this category.**

**Of all of them, of all the five, this one, I think, has been best studied. We are pretty familiar**

**with the need for plain language consent forms, advance directives, supplementary educational measures, surrogates, advocates to assure that the candidate subject's values and interests are adequately taken into account.**

**Let's go to juridic subordination.**

**(Slide.)**

**In juridic subordination the question we ask is, is the candidate subject liable to the authority of others who may have an independent interest in that participation? The compensating steps would include insulating the candidate subject from the hierarchical system to which he or she is subject.**

**For example, in the ACHRE study, the recommendations they made with respect to the military was first of all that officers be excluded from those sessions in which enlistees are being asked to volunteer.**

**Secondly, ombudsmen/ombudspersons be present at those sessions to ensure that voluntariness is adequately stressed.**

**In talking, for example, about children, children can fall into all five of these categories.**

**Talking about children, our discussions about -- the well known discussions about assent, for example, and I think the need for a private conversation with a kid. Okay. Just to ensure that**

**the kid is with the program in an appropriate way. All are ways of insulating people from the effects of juridic subordination.**

**Let's go to the next one, patterns of deference.**

**(Slide.)**

**Here we are asking is the candidate subject given to patterns of deferential behavior that may mask an underlying unwillingness to participate? Compensating steps: Devise a process that eliminates as much as possible the social pressures that a candidate subject may feel even if, in reality, they are not being imposed.**

**This morning you were talking extensively about women in Third World countries and what I would want to say about that is it reminds me of issues that we have in Hawaii quite frequently because there are many cultures in Hawaii that exhibit a deference to others in the family, especially where end of life decisions need to be made. And I do not see why something like that analysis cannot be used in the case of research as well.**

**When approaching one of these patients you try to do it privately. This is the -- basically the advice I give to health care professionals when I do my teaching as a medical ethics specialist.**

**Number one: You explain the situation to**

**the patient. The choice that needs to be made. And then you say, "Look, some people like to make these decisions by themselves and other people prefer it when, you know, an eldest son or husband or a grandfather makes these decisions. Please help us to understand how we can best serve you." So you are leaving it to the patient basically to show his or her cards.**

**I am a Samoan but how -- and Samoans always do what the Matai, the chief, tells them to do. Okay. But am I traditional Samoan or a marginalized Samoan or a Westernized Samoan? Okay. Do not assume that because you have a Samoan you have somebody that is only going to do what the Matai tells him to. You give people the opportunity to show their cards and to let them decide who the decision maker is going to be. I think that is a nice compromise between autonomy and the patterns of deference that really are exhibited in certain kinds of cultures.**

**Medical exigency. Let's go to the next one.**

**(Slide.)**

**Does the candidate subject have a serious health related condition for which there are no satisfactory remedies? The question I would want to ask -- a lot of the issues in this by the way really focus on the voluntariness of the subject and I think that is a mistake. If I, for example, have a really**

**serious infection that is going to kill me, and I go to the doctor and he says, "You need an antibiotic," and he gives me the antibiotic and I am cured, I cannot get out of paying the doctor's bill on the grounds that I was going to die if he did not give me the drug. I am in a really poor situation but I can make a decision and it is a rational decision.**

**However, if the doctor says, "Okay. I have got an antibiotic here that is going to -- it cost me $3.50. I am the only doctor you can go to and I am going to charge you $2 million for that shot." Okay. Then it seems to me we can start having reservations but notice it is not the voluntariness of the choice. Okay. It is rather the nature of the agreement and that is what I want to direct your attention to.**

**Yes, there is a vulnerability there in terms of medical exigency but the question we have to ask is given the interest and aspirations of both parties is there a fair division of the benefits and burdens of cooperation, or put in another way does the arrangement fairly reflect the needs and aspirations of both parties? And that is really a species of justice that we are really talking about. So we have to ask whether the arrangement really adequately reflects the needs and aspirations of both parties.**

**(Slide.)**

**Of course, here is where the therapeutic**

misconception arises. The research subject driven by a false but persistent hope may enter the study with an unreasonable expectation of success.

I am reminded of -- I refer to it in the paper -- Christian Barnard's lions and crocodiles example, which I think is really useful here. Okay. Often people in a state of medical exigency are facing a really bad outcome and they are willing to -- and they are rationally willing to take much more serious risks in order to get out of it.

Let's look just for a moment, let me just say that my -- that there are two ways of approaching the therapeutic misconception. Okay. One is to beef up somehow informed consent so that somehow the subject knows that there is no expectation of benefit or there is no reasonable expectation of benefit.

I have to say that both of the parties sitting here just a few minutes ago in my opinion reasonably anticipated the possibility of benefit.

So the other is -- and this is what I am going to recommend -- that you try as much as possible to make the subject's belief reasonable. In fact, that is what you were talking about this morning. You were kind of groping for that in some of the discussion.

Let's now look at a Phase I clinical trial.

(Slide.)

**Phase I clinical trial. A fairly standard one in which the principle of maximum therapeutic benefit is not entertained. For a trial like this you see at the bottom T1, T2, T3 up to T6. Okay. You have six cohorts entering at different dosages. The large lines, this is why I wanted -- let's see if I can somehow reach this here. Am I lit? No, nothing. Okay.**

**I will tell you what -- I can do --**

**DR. SHAPIRO: You are welcome to come up here if you would like to do so.**

**PROFESSOR KIPNIS: I can. Okay. I will talk very loudly.**

**DR. MESLIN: Just sit right here.**

**PROFESSOR KIPNIS: Okay.**

**DR. SHAPIRO: Just press the button.**

**PROFESSOR KIPNIS: This is a standard diagram of a fairly standard Phase I clinical trial. There is a little dot there. Patients come in at this dosage level and they will basically stay on it until their disease progresses at which point they are taken off. A second cohort of patients will enter at this level provided that serious adverse consequences have not occurred here. A little bit later on a third cohort enters at a higher dosage and so on until the study ends. The study ends. Okay.**

**Now a couple of things. The guys down at**

**the bottom are typically receiving theoretically subtherapeutic doses and if there is a placebo arm there are some who are receiving theoretically sub-subtherapeutic doses. Okay. The people at the top are generally in a therapeutic dosage range at least theoretically but the study ends here. Okay. So there are at least three ways in which you can fail to benefit.**

**One is you are put on a placebo arm in which case you are not going to benefit although there is something really interesting about a nontherapeutic study -- think about this -- with a placebo arm. And that is an oxymoron if you think about it because if I believe it is going to make me better then I am violating the therapeutic misconception. You have not done your informed consent job well enough.**

**And there are more things wrong with this.**

**Secondly -- first is I am on a placebo arm. Secondly, sub-subtherapy. Okay. And, thirdly, even if I am benefitting, as we have seen, the study can end.**

**Let's now ask what would this study look like if it met the maximum therapeutic benefit standard.**

**(Slide.)**

**A couple of differences. One is if my illness progresses, let's say I am on D1 and my**

**illness progresses. I can move up to a higher dosage level (a) provided that a second cohort has cleared that dosage level without receiving serious adverse consequences and provided that my own disease is, in fact, progressing and I am not getting any better. Okay.**

**And so after this period, let's say after the second cohort, after the third cohort completes its period, okay, groups on the second cohort can, in fact, move up if they have not yet improved. And here is the most important thing, okay, the study goes on. Okay. It continues beyond the endpoint. Okay. As a standard event. Okay. There are only four ways in which you come off the study. Four exit processes.**

**Number one, you die. Number two, serious adverse effects begin to appear and we just are not comfortable putting you on that with those serious adverse consequences. Number three, you get cured. Okay. And number four, you quit. Okay. You leave on your own. Okay.**

**Now after doing this, after putting this thing together -- let's go on to the next one. Okay.**

**(Slide.)**

**It began to occur to me that there were also scientific advantages. Not only does this give you all the scientific data you would get in the first**

**study, you would have a whole new collection of data, okay, to chew on.**

**Number one, the usual Phase I clinical trial gives you dose related toxicity data. This maximum therapeutic benefit trial gives you duration related toxicity data. Okay. Plus -- and I kind of like this, okay, at the end of the Phase I study since the individuals who are benefitting or who might be benefitting will carry on with the drug. You move immediately, okay, into something like a preliminary Phase II study which potentially can improve the rapidity of actually demonstrating the efficacy of drugs like this.**

**I am inclined to think that if efficacy is shown the drug companies will be so pleased with this, the possibility of marketing what will, in fact, be a profitable drug that they would not mind the necessity of having to continue to provide the drug free essentially to what, 20, 30, 40, less than 100 patients typically on a Phase I clinical trial.**

**So what I would like to say is in addition to being scientifically sound clinical trials should also be designed to maximize the likelihood of subject benefit. That is the additional standard I would want poked in to the notion of a clinical trial.**

**Subjects should be assured -- and this is**

**the guarantee you are providing them -- that they will have a chance of benefitting from participation if it turns out that the drug is safe and effective. Okay.**

**What we have right now is that even if the drug is safe and effective -- and this is what the informed consent, I think, ought to look like if you want to take that route. We have to say to patients, look, first of all, you might not be able to -- you might not be getting any drug at all. You might be getting just a placebo. Number two, even if you are getting the drug it is likely to be administered at a subtherapeutic dose. Number three, even if you are improving on a therapeutic dose the study will end and you are on your own.**

**That is one route. I do not know how many people would be willing to volunteer on that basis but it seems to me the other route is actually to design the study so as to take into account the needs of patients, the needs of these particular patients.**

**Let's go to the next slide, please.**

**(Slide.)**

**I will just say a little bit about allocational disadvantage. Essentially it is very similar to medical exigency except the goods are really socially distributed goods as opposed to health. The question is, is the candidate subject**

**seriously lacking in important social goods that will be provided as a consequence of participation in research? And this, of course, includes access to health care.**

**Compensating steps ensure that given the candidate subject's precarious position the exchange meets applicable standards of fairness, that it does not unjustly exploit the subject. Now that is a topic that I really -- I think it needs a lot more exploration than I can give it here and, in fact, than I can give it, period.**

**Let's go on to the last one.**

**(Slide.)**

**And these are three recommendations. One is insofar as possible scientifically sound studies on medically exigent patients should be required to meet the maximal therapeutic benefit standard. This recommendation does erode the traditional separation of research and therapy and I want to kind of underline that.**

**I think that in cases of medical exigency where there are no standard treatments that are safe and effective, and I would very much like to see a list of medically exigent conditions. I think that would be really useful. The distinction between research and therapy vanishes.**

**I am reminded of Ambois Poiret, the surgeon,**

**who was in Northern Italy in 1536, when large numbers of men presented with gunshot wounds. The standard of practice in those days was to cauterize the wound.**

**Poor Ambois Poiret ran out of oil half way through the men that he was supposed to be -- whose limbs he was supposed to be amputating. He ran around trying to get the oil and was not able to. And so half the men got cauterization, the other half basically had their limbs amputated and bandaged, and he went to bed that night fully expecting the next morning to awake and discover the second group all dead.**

**It was believed that gun powder was poisonous at the time and you had to cauterize the wound in order to eliminate the effects of the poison.**

**When he wakes up he discovers that the men in the second group are all doing really well. They slept well. No pain, no infection. The first group, infection, slept badly, lots of pain. He takes a while but he publishes the results. Okay.**

**That is an example of medical exigency. Okay. But what Poiret does, it seems to me, is he is mindful. He reports the results. Okay. He is careful. Okay. He has no other choice. There is nothing else he can do. He does not go to the IRB asking for permission to do a trial. Okay.**

**And there are other examples as well where I think this can be done and if we think about it in a careful way it seems to me we can understand how to approach these conditions in ways that really do respect both parties.**

**We need to give further attention to fair compensation for allocationally disadvantaged research subjects. In particular, I am thinking of something like workmen's compensation for injuries sustained, at least for some of the people, injuries sustained in the course of research.**

**And then, lastly, and this is probably the most important recommendation that I am making, we need to supplement or replace the subpopulation focus in bioethical treatments of vulnerability with an analytical model.**

**Thank you.**

**DISCUSSION WITH COMMISSIONERS**

**DR. SHAPIRO: Thank you very much and thank you for sending us your paper in advance.**

**Jim?**

**PROFESSOR CHILDRESS: Ken, thanks very much. A couple of questions. One is you mentioned that it depends on the day as to whether you have five or six categories. I am curious as to what other types you considered and rejected. For instance, it struck me that power, power differential might well be another.**

**That might not be the same as either the allocational disadvantaged or the authority, juridic authority as you spell them out. That is the first question.**

**The second one has to do with a kind of -- your emphasis on connection or what 38 meetings ago -- since this is our 42nd -- we heard from Sylvia Fisher, who was talking about understanding vulnerability in relational terms. Now you have focused on it more in terms of the connection between consent and permission but you have also in your slide on the two directions worked with a relational model that has more similarities with some of the things she was trying to do. You have precariousness in the subject and then others who are disposed to capitalize on this weakness. Now my question for this one is whether you consider those both to be necessary conditions for a state of vulnerability. So if you would not mind defining both of those.**

**PROFESSOR KIPNIS: Okay. Let's talk about power first. Okay. I mean, I went through a number of examples of power but all the ones I looked at, okay, resolve themselves either in one of those three ways. Allocational disadvantaged occurs when I have got control over things that you need. Okay.**

**For example, the Willowbrook case is interesting because the guy who was deciding whether or not a parent's child entered Willowbrook was also**

**the one who was running the experiment. Okay. And so -- at least that is my recollection. And so he was creating the allocational disadvantage at the same time as he was taking advantage of it. So that is a kind of power but really we are looking at two things. Juridic authority over who gets in and who does not get in and the ability to create scarcity. And that is kind of an interesting case.**

**The other example is where people are objects of deference and you do not even need to -- sometimes you are not even aware of it. I mean, there is deference to tall men, for example. You know, we might not even be aware of that type of deference.**

**Does that answer your question?**

**PROFESSOR CHILDRESS: The power is not the -- on the first question, the power is not -- that was just one example throughout. What would be the other things you would consider? What else tempted you in the analysis?**

**PROFESSOR KIPNIS: Okay. I had a lot of trouble with pregnant women, okay, and I -- they do not appear on this list. Okay. And I am not sure -- it may be -- I am ready to face the possibility that pregnant women are not a vulnerable population. Fetuses or the adults that fetuses might become might be but maybe not pregnant women. Okay. Although I**

**struggled for a long time trying to find the place for them it did not pan out that way and I still do not know what to say about that.**

**The one that came up this morning, okay, was people living in governmental situations that do not provide adequate protection for research subjects. Okay. We rely on IRBs and clearing mechanisms constantly to protect us from unreasonable research and when you are dealing with Uganda -- I admit I was not thinking about Uganda when I wrote the paper. Okay. But if we are looking at Third World country which does not have the infrastructure capable of providing the protections that we take for granted in this country, I think it is reasonable to call people living in such an environment vulnerable.**

**Okay. And I do not have a name for that. I would love to have another nifty name. Political vulnerability maybe. Okay. But I have not settled on one and it seems to me in relationship to what you were talking about this morning that is one topic.**

**I forgot the second question. Something about consent and permission.**

**PROFESSOR CHILDRESS: Whether given your two directions you view both precariousness in the subject and the disposition on the part of others to capitalize on the weakness as both necessary conditions for having a state of vulnerability.**

**PROFESSOR KIPNIS: Yes. That is where it starts being a problem. That is we do not care too much about babies who are exquisitely vulnerable because most of them are adequately well protected. There are people that are, you know, going to be taking care of them. But when they are -- with respect to -- and I do not want to besmirch researchers. Okay. But it is clear researchers need to do research. Their careers really depend upon it.**

**And it is also clear that the background that researchers have typically does not equip them with the kind of sensitivity to these issues very often and so I am not so much worried about evil researchers as I am about ones who are not sufficiently sensitive to the various ways in which subjects can be vulnerable. Okay. And it seems to me that is the danger. It is almost a lack of kindness. A lack of sensitivity.**

**And it is my hope that by laying out in a really careful way these different types of vulnerabilities researchers -- I am thinking about researchers as being the threat here. Okay. But it may not be an ill-willed threat. It may be a threat that emerges really out of negligence. A certain lack of appreciation of the way people in a Third World -- the way things work in a Third World country or the way the world looks like to a six year old,**

**for example.**

**Does that help?**

**DR. SHAPIRO: Trish?**

**PROFESSOR BACKLAR: I am very interested in your -- could you say a little bit more about why you did not -- it is not that I disagree with you but I am interested to know why you thought that pregnant women were not vulnerable.**

**PROFESSOR KIPNIS: Well, okay.**

**PROFESSOR BACKLAR: Would you explore that a little bit and then -- okay.**

**PROFESSOR KIPNIS: Okay. First of all, okay, they are vulnerable. Okay. I mean, obviously they are -- we all are and some of us more than others and probably pregnant women are more vulnerable. Okay. But now the question is are they vulnerable in a way that needs to be taken into account in the context of research and what is it about pregnant women, okay, that requires us, okay, to take their interest into account?**

**Certainly the informed consent process would require us to say not only what the consequences are going to be to the woman but also to the pregnancy and to the offspring. Okay. So, you know, we are getting all that in and we are okay on that but that does not add anything to what we are -- it seems to me -- already required to disclose.**

**PROFESSOR BACKLAR: But it was interesting to me that in your paper you used the woman in labor as an example of a time where you could not ask somebody to participate and so the issue is that the woman herself is not vulnerable but her condition may move her to be vulnerable in the same way when you talk about medical exigency.**

**But there is also another aspect here which is not quite clearly explored and it is unspoken, and that is the issue of dependency, which you do not add in to your list even -- you -- one reads it in there in certain of your groups and there is that aspect which is unspoken about our attitudes towards women who are pregnant.**

**PROFESSOR KIPNIS: Well, dependency --**

**PROFESSOR BACKLAR: That in some way we must take care of them.**

**PROFESSOR KIPNIS: Well, I mean, dependency, I think, would cash out either in terms of allocational disadvantage. There are things which a dependent person cannot get for himself or herself that he or she needs to rely upon others so there is that piece of it. Also patterns of deference, and the two of them come together in Stockholm syndrome. Okay.**

**And then also juridic authority where, in fact, I am legally subordinated to the individual who**

**is my custodian in one way or another. So if you have something else that you want to fit into dependency that does not -- is not captured by those three, I am eager to hear it but I -- it seemed to me I could handle it given the categories that I had.**

**PROFESSOR CHARO: Hand up.**

**PROFESSOR BACKLAR: I was not thinking of outside of it but it is a component of almost each of these categories and it is a unifying component.**

**PROFESSOR KIPNIS: Yes. It could be. Was that Alta's voice?**

**PROFESSOR CHARO: Yes.**

**DR. SHAPIRO: It is Alta's voice but we will go to Steve.**

**MR. HOLTZMAN: (Not at microphone.)**

**DR. SHAPIRO: You will wait.**

**Alta, welcome back.**

**PROFESSOR CHARO: I was here the whole time.**

**DR. SHAPIRO: Good for you.**

**PROFESSOR CHARO: I want to follow up on Trish's question because I have never really understood the part of the category of pregnant women as vulnerable subjects. I understand the impetus for calling fetuses vulnerable subjects but do you know what the history is of that particular --**

**DR. SHAPIRO: Particular -- I did not hear the last --**

**PROFESSOR KIPNIS: I can offer --**

**PROFESSOR CHARO: In subpart B.**

**PROFESSOR CAPRON: I can offer something on that, I believe. There were articles written about studies done of pregnant women in labor which indicated that their consent was sought and obtained for studies which after the fact they described as not things which they realized they were subjects and so forth and it may well have been in addition to the issue of the fetus as subject. Those studies which were in the literature and talked about in the 1970's.**

**Bradford Gray, for example, had a lengthy description in his work of such studies. He may have treated pregnant women -- and there the category is not distinctive. It is simply people who because of their medical condition, and there it is one which is quite exigent in terms of proceeding with the delivery process, would not be in a position to weigh choices, and I think the argument also was that that was an example where it would be possible to have adjusted the research process to have consent obtained prior to labor.**

**PROFESSOR CHARO: Thank you. Thanks.**

**PROFESSOR CAPRON: That is all I know of, Alta.**

**DR. SHAPIRO: Any other examples anybody**

**wants to offer for Alta? No.**

**Steve?**

**MR. HOLTZMAN: I wanted to ask a question about the therapeutic misconception section of your talk but it also seems to me that we can on this last point that -- I think your analysis points to that, there are different senses of vulnerability. There is the sense in which we think of those who are vulnerable equal those to whom we owe a special duty of care.**

**And so insofar as a woman was pregnant and there was more than the woman at stake but the fetus, there was a sense of a special duty of care before, for example, you subjected them to a trial because of potential harm to the fetus.**

**I think it is just the illusion of those things, and that the analytical framework here gives you a way of saying is this woman in virtue being pregnant, vulnerable, and you go to -- that -- the special duty of care does not arise in the relevant sense of vulnerability. It is more things like is she feeling a social pressure to participate in this because she thinks she has as special responsibility and that --**

**DR. SHAPIRO: The focus here, as I understood it, Steve, is on the efficacy of consent. I think that is how you phrased it.**

**MR. HOLTZMAN: That is exactly right. That is --**

**DR. SHAPIRO: And that is why you have it hard fitting just in that way.**

**MR. HOLTZMAN: In your section about the therapeutic misconception, I am not sure I understand your analysis so let me -- you pointed to the two women who preceded you and said they certainly were rational having failed standard therapy to say what is out there in the experimental world. So it is not -- they are not suffering a therapeutic misconception particularly if they say we know that 90 percent of drugs fail but what the heck. Right?**

**PROFESSOR KIPNIS: Yes.**

**MR. HOLTZMAN: So I am trying to understand -- then you went to your diagrams of how to change a trial. I guess clearly, first off, you are calling it a Phase I but you are assuming this is a Phase I that is not taking place in a normal healthy population, which is in fact where most Phase I's take place. You are specifically dealing with the case of a Phase I, for example, in a cancer trial.**

**PROFESSOR KIPNIS: Pancreatic cancer.**

**MR. HOLTZMAN: Pancreatic. Okay. And I am wondering how much you are trying to generalize here because I can think of many therapies where the design that you advocate is irrelevant. So I am**

**trying to understand what you are trying to bring out and how much we can generalize from it in a Phase I with people who have failed standard therapy, for example, for malignant melanoma. You do do an ascending dose trial in order to find the MTD, the maximum tolerated dose.**

**PROFESSOR KIPNIS: Right.**

**MR. HOLTZMAN: Okay. You do not start off at a dose, you do not do a placebo control, all right, so that is an irrelevance in this context, right. You do not start off with a dose that you have reason to believe based on the animal data will not be efficacious.**

**You started -- your first dose is one where you think there is potentially a therapeutic effect and you are trying to rapidly get to the MTD.**

**PROFESSOR KIPNIS: I have seen studies that do start below the theoretically efficacious dose. You are concerned about adverse effects and I think they kind of like tip toe up.**

**MR. HOLTZMAN: No, no, you start below the -- what the MTD but you do not start below what is something which you think will be therapeutic.**

**PROFESSOR KIPNIS: Well --**

**MR. HOLTZMAN: You do not start at a dose which you say is likely to be not efficacious in such studies.**

**PROFESSOR KIPNIS: All I am saying here, okay, is that after we design the science, after we design a valid study, okay, and that is critical. I am not asking, of course, to back away from there. Okay. That the IRB require the investigator to put the patient's interest in recovery on the radar screen. Okay. And design the study in such a way that if it turns out to be a safe and effective approach, okay, what happened -- what we have been talking about happening will not happen. Okay. The patient can progress. The patient can continue in the event that he or she wants to and the drug is not harming them. And that is the major difference. That is the major difference. It solves some of the problems we have seen earlier today.**

**DR. SHAPIRO: Thank you. Other questions, other comments and questions? Larry?**

**DR. MIIKE: Just a comment. I found your approach useful in the sense that when one looks at the Federal Register and sees what are vulnerable populations, you just sort of shake your head. I mean, there is such a mishmash. They have no rationality in being put together. So just in terms of our study it seems clear that we cannot steer away from identifying some subpopulations because that is the way it is but it would be useful if we have such guidelines such as what you have suggested for IRBs**

**or researchers when they do a particular experiment and have questions about special precautions that there can be some guidelines that they can follow.**

**DR. SHAPIRO: I agree with you that it can be useful. It does not -- if we adopt this -- or if one were to try to adopt it and see how far you could run with this kind of analytic framework, just taking the efficacy -- consent is one of the key issues. You are then left with the problem of deciding how it is you decide whether someone's consent is efficacious and that -- it seems to me it will inevitably lead you to try to develop categories since it is very hard to do in a case by case basis.**

**Nevertheless, I agree with what you have said, Larry. I think this can help us deal with it.**

**DR. MIIKE: I would say that the issue about whether there is true consent or not is a different question and I like the -- obviously you cannot do it for every research project but for those where there are serious consequences of participation I like Pape's idea or his implementation of a questionnaire that sees whether the research subjects really do understand. That was why I asked the first participant, Ms. Wilson, the question about did she understand the reason for the research.**

**DR. SHAPIRO: That is reasonable. I agree with that.**

**Yes?**

**PROFESSOR KIPNIS: If I were rewriting the standards what I might do is to provide an analysis of each of these, each of these categories, and then list the subpopulations where this particular vulnerability is likely to be found. And then couple that with the steps that should be taken in relation to that, and in that regard -- I mean, one of the projects that I thought might be really useful was actually developing a consensus document from researchers on the various strategies that they have used to compensate for cognitive impairment, for patterns of deference and the rest using something like the MCWIRB listserv, okay, and actually generating a long term project of developing a collection of strategies so that IRBs would not have to reinvent the wheel every time they faced one of these. They could look up the various procedures that might help.**

**DR. SHAPIRO: Marjorie, do you have anything else you want to address?**

**DR. SPEERS: No.**

**DR. SHAPIRO: Any other questions? Once again, I want to thank you very much for presenting the paper. It has been very helpful and very stimulating. Thank you very much for coming.**

**We are -- unless Eric has some logistical**

**advice, we are going to adjourn in five seconds.**

**DR. MESLIN: Two quick announcements. A reminder that the previously announced video that Marjorie mentioned is tomorrow morning at 7:30 and for commissioners who are going to dinner, please see staff who will arrange lifts for you.**

**Thank you.**

**DR. SHAPIRO: Thank you. Any questions? We are adjourned.**

**(Whereupon, at 5:10 p.m., the proceedings were adjourned.)**

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