40th MEETING

NATIONAL BIOETHICS ADVISORY COMMISSION

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I N D E X

P R O C E E D I N G S

OPENING REMARKS

DR. SHAPIRO: Colleagues, I would like to get this meeting underway. Thank you very much for being here. I think we have set a new record for NBAC. On the second day we start our meetings at 8:00 o'clock and we usually start about 8:30, twenty to 9:00, and here it is only 12 minutes after 8:00.

So I apologize to Professor Dickens, however, for us starting a little bit late this morning.

I am not going to -- although I have some opening remarks on the agenda I am going to restrict those to just really a sentence or two. We will be spending all of this morning on various aspects of, not only our oversight project, but on some subjects which really overlap between our international project and our oversight project, and you have -- of course, we will turn to Professor Dickens in a moment, and you all have his paper, "The Challenge of Equivalent Protections," and the issue of equivalency came up yesterday quite often in our discussion and, of course, we will be visiting that directly in a moment.

We will be speaking with Professor Dickens not only on the challenge of equivalent protection but other approaches to oversight of human subjects.

As you know, you have all seen the Tri-Council Report that was put out by our colleagues in Canada, and it is gradually being implemented as I understand it, but Professor Dickens will tell us more about that later. But as part of our oversight project, we do want to take a look at what other countries are doing, and see what it is that we can learn from them since an awful lot of good work is going on in other countries, in Canada in particular, but other countries as well.

Of course, we faced that problem yesterday on our international project with that marvelous chart that Stu -- wherever Stu is this morning. There he is -- made out, which was really quite extraordinary, and what we will be able to learn from that.

So why don't we just proceed directly to our business this morning and I want to begin by introducing and thanking Professor Dickens from the University of Toronto, not only for the material that he has provided us and the paper he has provided us, but for taking the time to be with us this morning.

We are very grateful to you for spending some time with us and look forward to our discussion. So why don't I just -- everyone has a copy of the paper that you provided us and why don't I just turn the microphone, so to speak, over to you and we look

forward to our conversation.

ETHICAL ISSUES IN INTERNATIONAL RESEARCH

THE CHALLENGE OF EQUIVALENT PROTECTION

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DR. DICKENS: Thank you. Could I begin by thanking you for the opportunity to be here and to join with you discussing an issue that is really of worldwide significance, that is how one promotes research, how one protects those who are intended to be subjected to it, certainly to its risks, and one would expect to its benefit, though risk and benefit do not always coincide, and that, of course, is one of the problems. More of a macro than a micro problem.

The initial question is, the focus of the intended protection, and if one approaches research from a medical setting, one thinks of the risks of harm from intended interventions; that is the medical model is very physiological and its psychological aspects are regarded as somewhat secondary.

If, however, one broadens the spectrum, one can see that what is at stake in research is not simply

the physical integrity of the individual. There is also the psychological, social, and cultural integrity. And if one is concerned with protection simply against physical risk, there is the danger that in giving protection against physical injury, one ignores the cultural insensitivities, the insults that can be inadvertently undertaken. This is why when one is concerned with research in foreign countries, something of the local culture has to be fed into the review process.

In the context of the Code of Federal Regulations, the emphasis seems initially to be on the process of review, and if one is concerned with equivalent protection, there is a natural tendency to suppose that the equivalency is in the composition of the functioning of the committees that review the ethics of research. Whether they are concerned simply with the ethics, whether they include a review of the science, is a matter on which views can differ in that some committee processes will accommodate both scientific and ethical review. Some will be concerned only with the ethics, supposing that another agency has signed off on the science or will sign off on the science.

So although it is trite to observe that there

cannot be good ethics when there is not good science, it does not follow that because the science is sound, therefore the ethics is sound. One does need both. And whether a particular committee is concerned directly with both, or whether a committee concerned with the ethical integrity of research will be willing to accept the views of scientists on the quality of the science, is a matter on which practices can differ.

The initial language of the Code of Federal Regulations, though, addressing equivalent protection speaks about the process of review. It does seem clear, though, that the intention is to go beyond the structure and functioning of research committees to address the substance of what is proposed.

The fact that a model -- an example, an instance of equivalent protection that the federal regulations contain deals with the Declaration of Helsinki, indicates that the intention is to go beyond the mere process of review.

The Declaration of Helsinki is expressed in relaxed language. It is not mandatory. It is expressed to be recommendations and are, in contrast to other documents, coming from the World Medical Association, which state that they are intended to be binding. The Declaration of Helsinki does not say

that. It does not use mandatory or binding language.

In addition, its provisions on the process of review are, at best, rudimentary if one looks at the language of the declaration. With regard to review, all it says -- and you will find this in my paper at the top of page 4 -- is that a research protocol "...should be transmitted for consideration, comment and guidance to a specially appointed committee independent of the investigator and the sponsor, provided that this independent committee is in conformity with the laws and regulations of the country in which the research experiment is performed."

Well, this is really quite basic and startlingly short of the detail in the U.S. Federal Regulations and for the regulations to say that this constitutes equivalency indicates that there must be more at issue.

The other provisions of the Declaration of Helsinki address matters of substance, that is that the protocol should reflect generally accepted scientific principles, there will be prior animal studies. Whether there should be is a wider matter but at the time the declaration was drafted, and this has persisted in the language, the requirement was of prior animal studies. Qualifications and supervision of

research personnel, prior risk to benefit assessment and, of course, the core issue of the subject's voluntary and adequately informed consent, protection of the vulnerable, and respect for privacy and confidentiality.

So what really is at the core of the Declaration of Helsinki is not the process of review, but the substance of protocols reviewed, and when the federal regulations from the United States address equivalent protection illustrated in the Declaration of Helsinki, this seems to deal with issues of substance, not simply the process of review.

If one considers circumstances in many countries, and I would not limit this to the so-called economically developing countries, the facilities for review fall short of the ample provision of expertise that exists in a number of economically developed countries. In particularly, of course, the United States. The fact that one can go to other specialists who are up-to-date with the state-of-the-art, who are disinterested but who have experience in the field, this is something that one tends to take for granted. One supposes this can be satisfied.

We know that, in particular research settings, this may not be the case. It is not true on every

campus of a university. It is not true in every city or state or province. And, in many cases, it is not true of many countries. That is, in a number of countries where important research is being undertaken, there simply is not a solid core of specialists to whom one can turn for the sort of review that is indicated in the Federal Regulations, so some compromises have to be accommodated.

If one has a limited number of top level research institutes, the sorts of institutes that one would consider merit funding, they are very dependent on a small core of people, many of whom will have been involved in some earlier stages of the planning of the proposal.

There may be investigators at different stages, not necessarily principal investigators. But a project would not have been developed within the country, without calling on the scarce specialized expertise. If then individuals have to be found who measure up to the standards of independence, detachment, in the U.S. Federal Regulations, they simply may not be there. It does mean then that some level of compromise on committee composition may have to be accommodated.

In addition, one has the problem of who the

lay people are going to be who have to be on committees. The U.S. Federal Regulations, as a minimum, require five members, including members of both sexes, at least one of whom is not affiliated with the institution or the investigators.

One can have concerns in many stratified or otherwise divided communities that lay people, willing to engage with the specialist elites who otherwise would be provided by university and government organizations, would be in the tradition of deference, that is the vocal intellectually independent people, politically and financially independent people, that in developed countries we suppose will be available. They may not be as available in a number of other countries. The question of the credibility of the lay membership could be a matter of some concern.

It could be then that, at the level of the process of review, both regarding specialist personnel and lay personnel, one cannot have quite the confidence in some settings that we are more accustomed to, certainly in North America.

If, however, issues of substance are adequately addressed, that is, if one has adequate protection for the freedom, the level of informed choice that those invited to take part in studies have,

then it could be that one could be adequately comforted that the degree of risk, physical risk, is being contained even though the actual process may differ from what we have come to expect in a number of more traditional research settings.

The initial point then is, that the focus of equivalence is not simply on the process of review. Indeed, certain compromises may have to be accommodated there, but that the core values of protection of the physical and wider integrity of those invited to take part in studies will be protected.

I will not take you through the legal analogy of so-called private international law and conflict of laws, except to say, that it does give us models of legal systems reflecting wider social and political systems being willing to recognize that they do things differently in other countries, and what they do is nevertheless acceptable. In that sense there could be some lesson to be learned from it.

The question of minimum values does become important because, if we look at the modern history of research regulation, it really goes back to the 1947 Nuremberg code and I think we can accept this as an international document although it was actually modeled on the United States experience. It came out of the

Nuremberg War Crimes Tribunal but this was not the prosecution of the Nazi leaders.

This was an adjunct commission that was conducted, within the zones of control of the occupying allies of Germany. This arose in the American zone and, therefore, there were U.S. judges, U.S. prosecutors, U.S. expert witnesses, and the core of the Nuremberg Code was closely modeled on the practice of the American Medical Association.

So in a certain sense one could say that the entire Nuremberg Tribunal was dynastic in that, although it was conducted by the allies in their own language, it was essentially conducted by the forces operating German sovereignty. German sovereignty, of course, was not taken after the war. It was operated by the four occupying allies.

The Nuremberg Code, I think, has acquired its international status, in the same way as the Hippocratic Oath, again of narrow, regional, even parties and origins. It is taken as a document of universal significance, in that other countries have taken the core principles of the Nuremberg Code, and have adopted it as being a correct statement of principle. Correct but incomplete in that the Nuremberg Code was dealing with the grossest of

outrages against individuals and against population groups, and issues such as confidentiality were not a prime concern before the Nuremberg War Crime Tribunal. And it was taken up by the World Medical Association to flesh out certain of the details, that is of bona fide reputable research with vulnerable people who could not give their own consent, such as children and mentally impaired people.

To that extent then, the rules have developed and they continue to evolve. In the United States, for example, developments requiring research on newborn children and young children clearly incapable of giving their own consent, or research on victims of head traumas, road traffic accidents and so forth. These are all areas in which one recognizes that research is necessary. Indeed, to obstruct or frustrate or deny such research itself, would be considered unethical.

It is perhaps worth reflecting on this point, because the emphasis in the U.S. Federal Regulations is on protection of human subjects, and if we go back to the scenarios that the Nuremberg Code reacted against, we can see how necessary protection is.

What may be obscured in the emphasis on protection is that the research itself has a protective purpose. That is at the individual level, at the so-

called micro-ethical level, one can protect people against the risks of research by excluding them from research, and if everybody is excluded, then everybody is protected against the risks of the research. But, of course, the goal of the research is to protect people against physical injuries and health impairments, and the research itself is part of a protective and ethical enterprise.

The emphasis on protection then is historically understandable but it is incomplete; that is, there has been a revival of the recognition that not to undertake research leaves people vulnerable. Perhaps we could best take two instances of this.

The fact that women historically were excluded from research, certainly women of reproductive age, has given us a present circumstance in which many women are prescribed drugs and buying drugs over the counter that have never been tested on women, certainly not women of reproductive age. And in that sense, those women are denied adequate protection against products prescribed for them and purchased from them, sometimes directed more to them than to males. To that extent, one now recognizes that the protection of women against health hazards requires that there be research on women of reproductive age.

Clearly if one knows that a product would be harmful to a fetus in utero, if it is a teratogenic, then one would exclude women of reproductive age, but otherwise one would not.

This creates the problem for those who serve on institutional review boards, IRBs, which in Canada we call Research Ethics Boards, REBs. The problem, is that if an unproven product may, in fact, be the next generations of thalidomide, then that ought to be picked up in research. That is, if the product is harmful to fetuses, then that ought to be shown in the research, that is, the harm ought to be done in the research.

The harmful effect of thalidomide was detected a decade or so after approval of the product by epidemiologists, who found an undue incidence of limb defects, and then traced back the common theme that the women were taking thalidomide. Why wasn't that picked up at the animal study stage? Why wasn't it picked up at the human study stage?

So the problem that one has is that, the goal of protection, which of course has Hippocratic origins of do no harm, is certainly true in the context of intended therapy. But in the context of research, risking harm, determining harm, is all part of the

enterprise, and if the harm is present, but is not picked up at the research stage, then it may be picked up, as it was in the case of thalidomide, after a decade of conscientious prescription and innocent use by people supposing a product was therapeutic but, in fact, was harmful to the children they bore.

So we can see in the context of women's health that protecting individuals against research may be effective at the individual level, but it leaves populations of vulnerable people at risk of unproven harms.

In addition, of course, the advent of AIDS, HIV research, has given us this new phenomenon of people demanding that research be done and that they be part of it. The idea of individuals demanding that they be recruited into research, of course, turns the whole Nuremberg setting on its head. The individuals protested that not researching the condition affecting them and costing them their lives, was a form of discrimination, not the only form of discrimination that the target group complained of but an aspect of it. They demanded that research be done and they felt that they were not protected in the absence of research.

In that sense then, although historically we

can understand the federal emphasis on protection of research subjects, not doing the research is failing to protect at a macro -- at a social level. The research enterprise itself is ethical and protective, and protecting individuals is an aspect of research, but the goal is not simply to protect individuals, but to protect vulnerable population groups through the conduct of research.

Going back to the legal analogy, there are some rules that cannot be compromised in international law. This is often put in Latin, the "Ergomnias" rule. There are certain rules binding among all people and they are not amenable to compromise.

And it could be that the Nuremberg Code gives us a certain sense of the minimum conditions of recruitment of individuals into research. That is, if they are competent, they should be given adequate information. Therefore, the exercise is their choice regarding whether they participate or not, and the conditions on which they participate.

If we go beyond Nuremberg though, the World Medical Association's Declaration and other international documents, the Council for International Organizations of Medical Sciences, a joint world health organization, UNESCO, -- they are functioning

only out of Geneva -- has codes on human subject research. A 1990 code and a 1991 document on epidemiological studies. They all go on to address levels of protection of vulnerable people incapable of giving individual consent, but for whose health protection research is required.

And although one may look at overseas models of research regulation and perhaps be willing to accommodate some compromises on the functioning and the structure of research ethics committees, there can be no compromise on rules that competent people should be able to exercise their own choice on recruitment. This is one of the nonnegotiable or noncompromised principles.

The issue that I am certain you have been engaged with, if not yesterday, then in earlier meetings, is the problem of apparently exploitive research sponsored in developed countries but conducted in developing countries that have few alternative resources to use of the test product. Now that is so-called placebo controlled studies where the alternative to the test product is that one has no product at all. This is where the language of the Declaration of Helsinki has proven problematic and the very process of changing this language is no less contentious in

present times.

The proposition in the Declaration of Helsinki -- and I will be brief because I am certain you are very familiar with this, more familiar than I am -- is that in any medical study every patient, including those of a control group, if any, should be assured of the best proven diagnostic and therapeutic method.

Well, to say that one can test the unproven product against the best diagnostic or therapeutic method makes scientific sense. The issue is whether one can, therefore, test products in settings, national settings, where the best proven diagnostic and therapeutic method is simply inaccessible, that is people simply do not have access. And there is the criticism, and one could understand the good faith of the criticism, that to perfect products, to improve products for developing markets, one should not undertake the economy and the exploitation of going to developing countries where the alternative to the test product is no product at all, and then conduct your placebo control at the cost of those who would have no access to the best proven diagnostic and therapeutic method.

I will not go through the full debate on this. As I have said, I am certain you are very familiar

with it. I will come to one, what I would propose as a credible resolution, a credible bottom line on this, and Dr. Robert Levine may have appeared before you urging his approach to this, which I would adopt. And that is, that what developing countries want is improvement over their existing situation.

One, therefore, has to test a new product against the normal level of revision they experience if, indeed, one is to test a new unproven product against the best therapeutic method that is alternatively available. There is no point in taking that research to a developing country, because it offers them nothing, when they have no access to the best therapeutic method. That is this exploitive research and ought not to be conducted in those settings.

What serves the needs of resource poor countries is to improve on their existing situation and, therefore, the unproven, the test product ought to be tested against what is their local alternative, not the alternative developed by the best that medical science can offer.

I think in that sense then, one can say that one does not need local input. One does have to have adequate review of the circumstances of the host

countries, and sensitivity to the culture of the host country, in order to ensure that the research is beneficial to the host country, that it serves the needs, the perceptions of the host country, and that it is not unduly a waste of their scarce resources, and that it does accord to their sense of priorities based on circumstances that they experience.

This relates to the risk to benefit assessment that is supposed to be undertaken. If one thinks in risk to benefit terms at a purely medical level, then there will be some hazards in the research, but the research is directed to health amelioration, that is the intended benefit, and although there is the apples and oranges equation that can be difficult, one can assess values that the intended, the prospective, the credibly prospective benefit does justify the reasonably assessed risk.

The Declaration of Helsinki and the CIOMS 1993 guidelines and also the 1991 CIOMS guidelines are more explicit, however, on the need to assess both risk and benefit in the context of the host country and this does require that a review be conducted by those familiar with the circumstances of the host country.

As I have indicated in research, there will always be some risk. There is never zero risk. One

wants minimal risk and, of course, one cannot make perfect anticipation of what the levels of risk will be. There is always the chance of encountering the unexpected, which may prove to be an unexpected tragedy, but one can make reasonable good faith assessments, on the best of prevailing knowledge, and be willing to learn, even ruefully, from the subsequent experience.

There is always going to be some risk. One does want to ensure that there will be some benefit. This does, of course, feed back to the earlier point of placebo controlled studies in resource poor countries, because to test an unproven product against an alternative they do not have, cannot be of benefit to them. It may be of benefit to others, and critics have drawn attention to that, and in that sense testing in their circumstances for a benefit they perceive and want would seem to require that there be local review.

Again what is a risk? It could be a relative matter. If we take anecdotal data from countries where HIV infection is highly prevalent, countries of East Africa, for example, one finds that women of considerable intelligence and perception are willing to initiate pregnancies when they already are affected by the virus, knowing the risk of transmission to the

child, and one wonders on what rational grounds they act.

A number, though -- and there is anecdotal literature on this -- have said that the risks identified of pregnancy while HIV infected, the risk to the woman, risk to the child, are not greater than the risks that they ordinarily face in developing the families that they want. And in those circumstances, although we might be aghast at the level of risk that people consciously run in their comparative circumstances, they think that risk is not extraordinary, and in that sense, they are willing to take risks to advance the goals of their own lives and their own families and their own communities.

In that sense then, what we see as high risk, others may see in more moderate terms. Risks that we minimize or fail to recognize at all, could be considerable in the comparative circumstances of other countries. So one does then require that there be some competent capacity for review in the host country.

We have to take account, though, of the consideration that the risk is not purely physiological. That is, that the risk in medical research and clinical research tends to be perceived in medical clinical terms, but there can also be risks of

insult, offensiveness to religious traditions, cultural traditions, social traditions and customs. An account does have to be taken of that. How one can offset cultural insensitivity and risk by accommodating wider levels of physical risk again is one of those difficult assessments. It is one of the apples and oranges equations that have to be made and one cannot do more than require some experienced judgment in determining a common set of values that would be able to balance physical risk and social/cultural risk.

There can also be the need to accommodate practices that developed countries find offensive. In many settings one finds that it is improper for matters of sex to be discussed between strangers of the same or of both sexes. That is, one does not discuss the intimate details of human reproduction with members of the other sex, and in that sense, even within families. It could be that sexual issues, issues of sexual function and reproductive capacity are not discussed even between husband and wife. The wife may discuss it with her female family and friends. He may discuss it with his family and friends who are male, but they do not discuss it with each other, and that is something that has to be accommodated in the process of a review and perhaps in the process of informing. One has to

have those levels of sensitivity.

We are also familiar with traditions in which the husband of the family would be the decision maker, and the wife's duty would be one of obedience, but not one of independent autonomous decision making. And it could be then that, although we are accustomed to it being otherwise and require that it be otherwise, to impose this cultural preference, although we regard it as self-evidently right, on those to whom it is not self-evident, can be a source of some difficulty. And, again, if the research itself is worthwhile -- if the research serves a beneficial goal protective of a whole community, then one may have to accept that, that community at least for the time being will function in accordance with its own traditions and not ours.

There is an issue that the paper addresses. This is at page 19. It is a recent U.S. development and may prove to be transitory. But that is, the limitation on the sort of research that the U.S. can fund in other countries, where the volatile, apparently insoluble, issue of abortion is concerned and I address this on page 19 of the paper. Foreign research protections are compromised by U.S. requirements.

We accept that if health professionals and others feel that a certain regime is compromising the

health interests and the wider interests of a community, then physicians in particular as advocates for their patients will say so. The American Medical Association, for example, requires conformity with the law but it also requires that doctors speak out against a law that they think compromises the health and wider interests of those for whose health they care.

That political advocacy against restrictive laws is compromised by existing U.S. legislation. This is the appropriations measure that liberated funds with which the United States pays formerly unpaid dues to the United Nations; part of U.S. abortion politics has played into the area. A condition of congressional release of the funds is that there be limits on their use for reproductive health services, not limited necessarily to abortion issues, and that nongovernmental agencies in other countries that receive U.S. funds not use those funds or their own funds, for certain aspects of abortion advocacy.

Not everyone will accept that abortion advocacy is necessarily protective of individuals. But if we take prevailing doctrine in the United States, the freedom to participate in political civic society, the capacity, if not obligation, of health professionals to advocate at a public level in favor of

those whose health they serve, is taken as an important protective value, protective of physical and also political freedom and integrity. However, the legislation in the United States concerned with finance, concerned with appropriations, prohibits the use of U.S. funds and also private funds by recipient nongovernment organizations in other countries in this area.

Without elaborating the point, I think that one would have to conclude that, the U.S. Federal Regulations are restricted by subsequent inconsistent U.S. legislation, and in that sense, one has to accept that the equivalent protection that the federal regulations are otherwise directed to, would have to be limited to accommodate the provisions of the appropriations legislation. That is the ordinary proposition that earlier law is subject to amendment by later inconsistent law. That may not be the entire answer. This is something of a more legalistic character and perhaps I should not elaborate on it now. Not least because other views may be held by lawyers around the table.

The question of compliance with both U.S. regulations and foreign regulations is an important matter because, even though research is to be funded

and conducted only in other countries, in foreign countries, it could be that U.S. personnel are sufficiently engaged as principal investigators, or in other capacities, that they have to satisfy the requirements of their own U.S. based IRB. In that case, there may be a double or duplicate review.

The problem arises on analogy with the importation of drugs and medical devices into countries that do not have their own regulatory authority, because they do not have any indigenous drug industry, or any derivative of drug industry. I say that because Canada has no indigenous drug industry. All of the drugs tested in Canada come from brand plants of companies located in the United States and Europe.

A number of countries then are accepting that the products, that may be imported for therapeutic and other use in their countries, are developed in the more sophisticated scientifically advanced environments of the United States, Germany, Switzerland, France, the United Kingdom, the Netherlands and so forth. That they would simply have a so-called country of origin rule in which, if the product is available for use, therapeutic use in the country of origin, then it will be accepted by the potential importing country. The supposition being that, an adequate level of scrutiny

and protection of consumers has been established in countries where the products are produced and marketed, and other countries do not have to go through their own testing. If the country of origin approves the product, then potential importing countries will accept it as well.

And there may be a tendency to conclude that, if a research protocol satisfies the demanding monitor criteria of the U.S. federal regulations, then adequate protection is in place and a country does not have to undertake its own independent scrutiny. If it can be tested in the United States, then it can be tested in the intended host country.

I would suggest that this not be an acceptable doctrine at the level of ethical scrutiny. If one takes into account the requirement of a risk to benefit assessment, and if one takes into account the wider dimensions of both risk and benefit, one can see that many assessments have to be peculiar to individual host countries. That is, the perception of risk, the level of risk, the reality of risk could be quite different. The potential for benefit again could be different at both ends of the scale. The immense benefits that perhaps other countries in which a product are developed do not receive, are perhaps a frustration in

achieving a benefit in a given resource poor environment that in the United States would not exist.

To that extent then, I think it is a reasonable requirement that there be a local ethical review, and that the so-called country of origin rule for the importation of therapeutic drugs not be the relevant analogy for the purpose of ethical scrutiny and protection of the full spectrum of interests of those invited to take part in studies.

The issue of research monitoring is very difficult in all settings, and although monitoring of research is an important component of protection, one finds that there is uncertainty, even in the developed environment, of what it is that one is monitoring. Is it the effect of research? Is it the disclosure process in which individuals are recruited? Is it monitoring that there is a proper balance of sexes in studies relevant to both sexes? Is it that there is monitoring of the age spectrum for products intended to be available across different age ranges? The question of what one is monitoring becomes a matter of significance.

The concern now, with adverse incident reports coming out of research, is clearly compelling and we

can take our routine newspapers to find instances of people seriously injured in the course of developing products. For example, in the context of gene therapy. But it is not at all clear that the existing structure of IRBs is adequate to deal with adverse incident reports. If one is dealing with a fully funded study, in which there is an independent monitoring board then a data monitoring board, will undertake this level of scrutiny. This requires expertise and it requires adequate resources. This is a funding issue.

Many drug companies will have research data boards, monitoring data boards, for multi-center studies, independent people who can break the code when it is not clear to those administering products which product they are administering. There are those who can break the code and monitor the effects of research and perhaps stop it, if it seems that a particular arm of a study is attracting an accumulation of adverse incidents, or that one arm is doing so spectacularly well that it becomes an ethical issue whether one denies that benefit to those who have been randomized to another branch of the study.

So we certainly have some models of very immaculate monitoring of research, but that is not the case with studies that are not the fully funded or

multi-center drug studies, and in many instances -- and I must confess I am being rather anecdotal now because of my own involvement with a research ethics board in Canada -- adverse incident reports are submitted that the nonmedical people have no capacity to understand. And, of course, one receives an adverse incident report from the part of the study that one's own institution is conducting and one has no sense of how this fits in with statistics from other centers.

So one has to ask people, and the people that one asks may be independent specialists, but not uncommonly there are the investigators themselves, and so the research ethics board is dependent on investigators giving the research ethics board information about how well the study is doing. That obviously is not monitoring by the REB or by the IRB of the investigators, that is the investigators feeding their own perceptions, their own unconscious/subconscious biases perhaps into interpretation of an adverse incident report.

So there are concerns, not limited to developing countries or host countries, about just how research is monitored and it could be that this is a wider matter of concern that you have been addressing.

The final point that I will make is concerned

with how one may proceed. That is what sort of international practice might evolve hereafter. We find that in some countries -- for example, the Nuffield Committee in England, which really functions as a privately sponsored national ethics committee -- has recognized that the existing international codes are written in somewhat abstract language that does not necessarily contain the experiences that one finds in the trenches of ethical review, and there has been a recommendation that there be not another code, since many already exist, but there be what the Nuffield Council described as an intermediate code really concerned with the practicalities.

It is not clear, however, in the amplitude of codes, international, national and discipline specific, what another code is going to add. It could be that one needs a better means to understand and operate the codes that exist. That is, if one could build the capacity in host countries to operate existing codes, and to achieve the protections that they are aimed at, then one could have greater confidence that protection is being achieved. And this is protection, not simply against scientific flaws or against undue physical risk, but protections against cultural insults and insensitivities that are all part of the risk that

studies present and that protections might be developed against.

I think many of you are familiar and, indeed, I gathered in a chat over coffee before today's session began, there already has been discussion around the table of initiatives to build capacity in developing countries so that their own personnel would be able to interpret and relevantly apply existing codes.

One could also note a recent criticism that the international codes we have, have come from a narrow and somewhat elitist origins, that are very Western in their orientation, and there is a certain scarcity of contribution to existing international codes by those from the countries that host the research that the codes aim to regulate.

And there has been the proposal that, if one had a capacity in host countries to understand the operation and the deficiencies of existing codes, then there would be better codes developed more directly by those who bear the burden of research in their own countries.

One might, therefore, consider -- this is the point on which I will end -- that rather than putting enterprise into developing yet another code, which, with respect, might be subject to many of the same

criticisms that have been recently cast against prevailing codes, one could give attention to equipping individuals of appropriate backgrounds with training in prevailing codes, and the evolution of codes, so that one would have future confidence that codes had been developed that were relevant to the sensitivities in the host countries, and then, that the codes could be adequately operated through an educated leadership in countries familiar with the needs of scientific review, review across a spectrum of the health science disciplines, and also with awareness of local values and local priorities.

Thank you.

DR. SHAPIRO: Thank you very much for those very thoughtful and comprehensive remarks.

Why don't we just go to questions commissioners might have.

Mr. Capron?

PROF. CAPRON: Two questions for Professor Dickens.

The first is the emphasis you placed on the standard of comparison, the best proven method, was an interesting one. The way you linked that to the equivalency requirement, which was the major thrust of your assignment, arguing that -- as it seemed to me --

you could not just rely on the Declaration of Helsinki, in part, because that is only a document, you said on page 12, providing recommendations guiding physicians and instead you had to read it in light of the equivalency requirement.

And then you defended the position taken by Bob Levine that the comparison should be to locally -- present locally available alternatives. I wanted to make sure that I was reading your point correctly because the passage is to me slightly opaque and you did not address it in your oral remarks.

It would follow, therefore, that just as the comparison as to what is now available, on the argument that the study is designed to improve what is available, as you put it, that only interventions which have a reasonable prospect of becoming available, should they be proven by the research to be of value, would meet the criteria for acceptable research. Is that a fair conclusion to draw?

DR. DICKENS: It is fair but it is, with respect, incomplete in that one has two protective goals. One is protection of the individual against involuntary submission to risk and this is where the Helsinki standards, I think, are clear and enforceable.

The issue of beneficial interventions within the host country is a related issue, but it is protection at a wider level. That is, it is protection of the community against the injustice, the distributive injustice of being subject to risks for a benefit that they will never achieve. It is the interplay of the individual and the communal, the micro and the macro. The goal of the Helsinki Declaration, I think, trying to flesh out some of the dimensions of the Nuremberg Code is concerned with individuals. The point with regard to placebo studies is concerned with benefit to communities at large and the Dr. Levine point, I think, is that there should be benefit to host countries from studies at a wider -- at a social level. These are both aspects of protection but they are different aspects. The individual and the communal.

PROF. CAPRON: Well, I guess -- let me just read to you the sentence from your paper that has left me confused, and I am afraid your response now has not removed the confusion. It is on page 13 and I -- you know, I am not reading this the way we would read one of our own documents because we are worried about the wording and adopting it. I am simply trying to have you help me because it seemed to me that the logic of your argument depended on this.

You said, "Conducting studies to contrast an investigational treatment with the best standard...", and that best standard I gather there is a reference to a worldwide best standard, "...in a research poor country would violate the principle of distributive justice, since research subjects in the host country..." that is to say that resource poor country "...would have few, if any, means to avail themselves of the treatment their risk taking has shown to be preferable."

Now doesn't that say that, unless there are going to be means, reasonable means as opposed to few if any means, for people after the study, to avail themselves of it in that resource poor country that it would be unethical to conduct the study there? Or am I misreading what you have said there?

DR. DICKENS: Yes. The point is that the risks that individuals were asked to take would be -- would result in an adverse risk to benefit assessment if there was no reasonable prospect of benefit to the community that they care for.

PROF. CAPRON: So what -- then my question, the follow-up question is, what then follows from that? If -- one can see it in one of two ways it seems to me. One, that it is a barrier to conducting the

research, and a research ethics committee in that country and a well functioning research ethics committee in the sponsoring country, should decline to approve the research.

The other would be, the research may be approved but there is an ethical obligation on the part of somebody, the researcher, the sponsor, the country in which the research is conducted, its government, the government of the country, which is the sponsoring -- the origin of the sponsor -- to provide the access to the materials at the end of the study and then the question to whom.

The latter seems such a huge and almost unmanageable obligation, that it seems to me that the conclusion would be rather on the former, that it is simply unethical in the first place.

DR. DICKENS: Yes. This is right. That is it would be for the local committee to make its own estimate of the likelihood and we suppose this can be done realistically, not simply optimistically, of the benefit that will come to the country and if the benefit seems to result immediately in developing -- in developed countries then that research should not be conducted in developing countries.

PROF. CAPRON: And what if the part of the

risk would include coming to the end of the trial and having been fortunate to be on the intervention arm of an intervention that proves to be useful, and where the subjects continue to have need for that intervention to derive that benefit? It would be withdrawn. Is that again something which you think that a research ethics committee should factor into its balancing of risks and benefits?

DR. DICKENS: Yes. Part of the negotiation between the product manufacturer and perhaps a contributor to the financing of the study and the research ethics board, the IRB, would be what is to be done for those in the study. If not the individuals, then the members of the community they identify themselves with of ongoing benefit. And if there is no credible undertaking, and often there will not be, then one could conclude that this is an improper study, in that this is exposing one population group to risks that will result in benefits to a different population group and this would seem to violate the basic principles of distributive justice.

Whether the research ethics board in the host country would take a more optimistic view is something that one would take account of, but in principle, in the same way as within one's own country one would not

target a particular deprived population for research, the benefits of which they would not realistically have access to.

DR. SHAPIRO: Thank you.

Diane?

DR. SCOTT-JONES: My question is on the same topic and it has to do with your discussion around page 13 in the text that you provided us. Here you are asserting that the goal is improvement of health over current conditions in developing countries, and you make the argument that it is unethical to test a new treatment against the best standard of care in a developing country unless persons in that developing country could afford the best standard of care. You argue that it is unethical to -- it is ethical to test against their current standard of care even if their current standard is no treatment whatsoever.

My question is whether that argument does not also apply to the new experimental treatment that is being tested in the developing country? So would you then argue that it is unethical to test the new experimental treatment in that developing country, unless you can show that persons in that country would be able to afford the new experimental treatment, and so are you then left in a position of not doing the

research in that developing country or being in a position of promising to provide the new experimental treatment to persons in that developing country?

DR. DICKENS: Again I think it would be more the former than the latter. That is to require product manufacturers, certainly of unproven products that may not, in fact, prove to be marketable or to require governments to give continuing commitments to provide a certain level of health care to overseas populations, I think, goes beyond experience and reality.

It is really for the local committee to make an assessment of what is the benefit and I have recommended that they be required to say what benefit they find from approving the study.

We have to recognize, of course, that there could be benefits to a resource poor country other than the provision from external manufacturers of products or external governments of health care supplies. It could be that a part of the benefit that one builds into the protocol is the training of local personnel to undertake health reviews, the training of local personnel to identify sources of health compromises. It could be that one trains them in their own country. It could be part of the package of the research is to bring them to the United States, or other developed

centers for training, so that the country is left with something of value from the enterprise. It does not have to be that the only benefit is in improved diagnosis or therapy.

And, in principle, one would require local people to focus on -- to be crass -- what is in it for them. If they think there is enough in it for them, then that is an assessment that one can respect. One does hope that they will be educated in the experiences and the criticisms that a lot of research to produce a marketable product in affluent markets has been conducted in populations that had no prospect of access to those improvements.

DR. SCOTT-JONES: Could I --

DR. SHAPIRO: I am sorry. Diane, go ahead.

DR. SCOTT-JONES: Okay. I would like to make just a follow-up comment and question because I think this line of reasoning is critical to the decisions that we have to make in writing our reports. I want to ask whether you would then require that the same persons who get the benefit of say going for the training, going to school, should they be the same persons who serve in the study and put themselves at risk in the research study? Should they be -- should that -- should the study participants be only the ones

who can then go on to get more medical training and then help the country in that way?

DR. DICKENS: No. The intention is that the research in the host country would be conducted with indigenous personnel, who have been adequately trained to conduct that study, but also to be a resource for their country when the study is completed. A resource perhaps using their skills in other dimensions. The expectation is not that the subjects of the research would be trained but that the investigators would be involved in the development of their skills at different levels. That is a cadre of trained investigators would be left in the country when the study is over.

DR. SHAPIRO: Thank you.

Alta?

PROF. CHARO: Bernard, my thanks, also, for the presentation. I wanted to continue the discussion about reasonable availability concluding a trial. So far the discussion has focused on hoping that host countries will be educated and aware enough to make a reasoned decision about whether to permit a trial where there has not necessarily been an emphasis on later availability through reduced pricing or continued provision to former study participants, et cetera.

And yet you make the point several times in your paper, that these countries are often in a poor negotiating position with regard to many aspects of trial design which, of course, makes one wonder how effectively they could insist upon this kind of continued availability.

Since that, as you have pointed out yourself, is linked to the degree to which there genuinely is a benefit to the host country population, a benefit that is great enough and specific enough that it offsets concerns about risks or exploitation, I find myself wondering about more prescriptive measures.

And, indeed, we were debating them yesterday as to whether or not there should be an obligation placed upon sponsors that is stronger than simply a notation that it would be virtuous to make this provision.

And I noted that, in Canada's recent 1998 Tri-Council statement, that there is commentary on Article 7 that the research ethics board ought to examine continued access or, if impossible, provisions taken to ensure adequate replacement.

I wonder if you could comment first on the thinking behind that provision in Canada, whether or not it was intended to become highly proscriptive, or

if it was simply that attention should be paid in the overall risk/benefit evaluation? And, second, whether you think under the kind of global circumstances in which these trials take place a stronger statement might be in order from one or another international or industrialized major sponsors?

DR. DICKENS: Yes. The first issue relates to the concluding point in the paper, and by introduction of the paper, that there is a questionable capacity in many host countries at the present time to engage in the review of protocols, particularly regarding the protection of research subjects that one wants and one does really have to develop that capacity. That is if one believes that there is considerable responsibility in the host country for decisions on participation, then one wants to insure that the ability to make those assessments is adequate, that is familiarity with expectations, not simply in the written language of codes, but some familiarity with the past experiences, both bad and good, of the conduct of research.

From the perspective of the sponsoring country, the IRB does have to address from its own perspective what is intended to be offered to the host countries, and if one thinks that the deal is too inequitable, then one might find that the research is

not appropriately located in a country that has no or little potential to benefit from the study. But this is where the different dimensions of benefit come in, as I have said before, not just benefit to those who took part but equipping the country. Again it relates to building capacity not just for ethical review but capacity for indigenous health monitoring and improvement in accordance with scientific and other information.

PROF. CHARO: May I -- I am sorry, Harold. May I just follow up?

DR. SHAPIRO: Yes.

PROF. CHARO: Bernard, with your permission, I would like to just push this one more level of specificity if I may. I can easily imagine a situation in which a host country has personnel who are quite well equipped to understand the background of international research, the way it is conducted, what can be expected. And they make a calculation that even though the results of the research, even if successful, are unlikely to be made available to any substantial portion of the population, because the pricing will be out of reach for the public health system, although it might be available to some minority who have private access. South Africa would be an example. But that

overall the sudden appearance of additional clinics and general health care at those clinic sites makes this a reasonably attractive prospect and they are willing to sign off.

And yet in this arrangement there is, in fact, no contemplation of any kind of continuing access for the study participants themselves, who may be drawn from the poor population that relies on the public health care system, nor for any long-term strategy to make the product available at an affordable price for the public system.

You are suggesting now that a research ethics board in North America should look at that and make its own independent balance of the risks and benefits.

My question is, number one, do you think that under those circumstances the host country's determination should be determinative or, almost 180 degree separate? Do you think that industrialized countries should insist that the sponsor, whether governmental or private, make such provision for access following the trial either to the study participants or in some fashion to a larger part of the population in the country?

DR. DICKENS: Yes. I think it is a legitimate goal to hope and to try to mitigate inequalities in the

circumstances of host countries. It could be, though, that it is unrealistic to require research funders to resolve the problems of social inequality in other countries. This could be a commitment at a national level. I am not certain that it can be credibly focused through the research enterprise.

And it could be then that some research would result in perpetuation of prevailing inequalities and local countries might think that there is sufficient advantage for them in the project to accommodate it, to host it, even though some social disparities will remain.

The concern, I think, of the U.S. based IRB is that those inequalities not be exploited in the research. Not only that the inequalities are not aggravated, but that one does not depend on those inequalities in order to target research in that country. If then one is not exploiting it, I think one meets ethical requirements even though one cannot credibly resolve it. It could be then, that that is the point at which the decision of local people that there is sufficient in this for their development ought to be seriously regarded and respected in that sense then.

The difference, I think, is between

exploitation or nonexploitation of inequalities in host countries that cannot be resolved simply through the research enterprise.

PROF. CHARO: But, of course, in this situation, although it is no longer an exploitation of the inequality between let's say the U.S. and South Africa, it is taking advantage of the inequalities within South Africa, because the tests will be done in a poor population where the benefit to them is the existence of clinics for other purposes, but the drug's availability, should it become available at all, would be for an entirely separate population.

So are we in a problem of infinite regress where we have to look at inequalities within the countries in which we are doing studies?

DR. DICKENS: Yes. This would be one of the issues that would be part of the negotiations between the potential sponsor and the potential host.

As I know you are aware, one rarely makes a decision simply on a protocol as submitted. Much of the ethical review process is negotiation bargaining and one's own values ought not to be compromised. Again the binding of Mongolia principle. But, also, speaking to the local people, seeing who the local people are, seeing how representative they could be of

those who will bear the burden of the actual research. Then this is where one would have to descend into a level of detail which could be where the real devil is and where there may be angels too.

PROF. CHARO: Thank you.

DR. SHAPIRO: Thank you.

Eric?

DR. CASSELL: I would like to stay at the same rich vein for a minute. Let's go to the trial, the actual trial that made a lot of the trouble, which was the HIV maternal transmission trial.

If I understand you, it was appropriate to do that research, without a placebo, because of where it was done. Placebos were -- I mean, other therapy was not available. The issue then is not, if you are doing that trial in that country should it be against a placebo, that -- the answer is yes because that is the standard of care that that country has and that benefits -- would not benefit the country to do it otherwise.

On the other hand, the question is, should the trial be done at all because it is taking advantage of the inequities in that country. So the ethical issue is not the placebo issue, so much as it is taking advantage of that population that the host -- that the

sponsor took advantage of the population and that that is the -- there lies the real problematic and that is something to be resolved both by the sponsoring country's IRBs or whatever and by the host country's IRB.

The host country's IRB could say, "Well, the benefit to these mothers, if there is going to be any, is sufficient to overweigh that." The sponsoring IRB might say, "Nothing could overweigh that," taking advantage of that. Is that what you are telling us?

DR. DICKENS: The initial question would be to identify the goal of the study. What is the purpose of the study? If the purpose of the study is to provide some better level of health maintenance for HIV positive women, who are considering pregnancy and who have access to no treatment, then the study could be appropriate. If the purpose of the study is to improve on existing therapies that this population has no access to, then this is not an appropriate site for that study.

DR. CASSELL: Thank you.

DR. MESLIN: Larry?

DR. MIIKE: Yesterday we had a discussion where we were discussing whether it should be an obligation or desirable, and we went through a whole

list of things like continue it -- if a therapy is beneficial, continued access to that for the study population, whether it should be extended to the community and then also whether capacity building should be undertaken in a host country from simple things like better informed populations to a whole distribution system for the drug.

Of course, we could not resolve that among ourselves. And from what I hear you are saying is that -- and correct me if I am wrong -- you take the longer view, which is those kinds of decisions are appropriate to be made, but they should be made by the host country representatives, and that the issue here is, take the long view about building the capacity within a country to do that and then, therefore, you still have the sponsoring country's IRB, which will have their say in it, too, but those kinds of things that we try to catalogue and say yes or no, are really just a host of things and you would rather set up the structure to make those decisions.

DR. DICKENS: Yes. I think it is worthy but, with respect, an unrealistic goal to think that the miseries in the world can be resolved by manipulation of research protocols and funding. It is an ideal that countries with few resources should be raised to higher

levels, perhaps the levels that in the developed countries we take for granted.

But that is a proposal of excellence, and there is a danger that the excellent could be the enemy of the good and the good could be the enemy of the adequate. It could be that, in host countries, potential host countries, they realistically see enough benefit for themselves to be involved in the study that it does not address all of the problems that were perceive them having.

DR. MIIKE: Right. We will never address the issue about those who think that it is still exploitation and we know better.

DR. DICKENS: Yes. A credible criterion of whether there is exploitation is the adequately informed judgment of those who are likely to be exploited.

DR. MESLIN: Diane?

DR. SCOTT-JONES: I am still thinking about your assertion that the goal is improvement of health over current conditions in a developing country, and that it is ethical to be less concerned about the benefit to the individual if you can show a benefit to the society generally in terms of new clinics that might be built, more medical students trained in that

country.

And I am looking for the consistency between this line of argument and other arguments that you present in your paper and I am thinking of page 9 where you talk about what is basically the issue of coercion that Arturo raised yesterday.

And you make the claim that, in resource poor countries that the prospect of getting funding from the United States may be so enticing that it will shift thinking from a risk benefit assessment to persons thinking that this study must be done because of all the other benefits that will accrue to the society so I, as a potential participant in the study, would think not about the risk and benefits to myself but that I may be helping to get a medical clinic for my country.

I believe around page 9 and 10 you disagree. You think that that is not an appropriate way for research to be approved in a developing country. Yet if you accept your other arguments, about the improvement of health overall, then it seems that that is what you would expect to happen, that persons sacrifice their own assessment of risk and benefit because they can help their country get a clinic.

Do you see some inconsistency in what you are

presenting around page 9 and what you present later around page 13?

DR. DICKENS: I am bound to say I do not. That is not to say that it is not there. The initial assessment is that individuals should not be invited to take excessive risks.

The point of page 9 is that if a culturally detached elite are involved in decision making that they may focus more on the long-term macro benefit and be willing to trade off the interest of individuals. This is where the so-called "ergomnias" principle comes in. That is that, one should not deal with vulnerable populations unless one has very careful safeguards, and that those who are capable of making their own decisions regarding the risks that they are asked to take, should be adequately informed and free to decide whether they want to take that risk for themselves for some benefit that may result, not necessarily directly to them, but to others that they care for.

This is not unique to resource poor countries. If I go back to the thalidomide example, and the provision in the U.S. federal regulations that there be inclusion of both sexes and that unless a product is known to be teratogenic, women of reproductive age ought to be included in the study, part of the

disclosure there, part of the decision each woman makes, is whether she is willing to risk her own pregnancy in order to find that an unproven product is teratogenic. This is all part of individual decision making.

At the collective level, at the moment, in the absence of secure capacity for independent assessment in many countries, one has to be guarded that those, in fact, making decisions today may be looking to a longer term benefit and be willing to trade off the interests of individuals.

If those individuals are able to protect themselves, I think one has a cohesive way forward, in that one is cautious from the sponsoring perspective of those who are making local decisions. And one, therefore, wants to insure again the "ergomnias" principle that individuals asked to take risk to their physical integrity cannot protect themselves.

DR. SCOTT-JONES: One follow-up comment. When you talk about people in other countries, particularly developing countries, as possibly being culturally detached elites, I certainly hope that people in our society do not look at our commission and think of us as a culturally detached elite when we are struggling with these very difficult issues.

DR. DICKENS: I think there is a sensitivity to it. I would refer to the critique of the origins of existing guidelines at the bottom of page 35 of my paper, where the point has been made that the people involved in developing international guidelines have not been representative of the world community. I say that as someone having been involved in drawing up these guidelines.

DR. SHAPIRO: Thank you.

The last question right now. Well, Ruth is next.

And, Alta, if it is a quick question.

PROF. CHARO: It is actually if I may.

DR. SHAPIRO: Do you want to do it right away or can it hold?

PROF. CHARO: It can hold.

DR. SHAPIRO: All right. Let Ruth go first and then Alta's short one and then we will change subjects here.

DR. MACKLIN: Bernard, at various points in answer to these questions you responded using the phrase "it is not realistic or it is unrealistic or we have to be realistic." And I think we all agree that pie in the sky guidelines or conclusions are not helpful if they are unrealistic.

So what I would like to know about your -- some of the views that you have been urging. For example, the role of the research ethics board or research ethics committee, both in the developing country, and let's assume for now that they are well trained and knowledgeable, properly capacitated, and the same role in the sponsoring country, in the U.S. or Canada or wherever, whether it is realistic to think that they will disapprove research. As I believe, at various points, you indicated that should be the tact. The unrealistic thing is to expect the sponsors, the industry and the government to be providing these products afterwards.

But the apparently do-able and appropriate response, I think, in answer to Alex's first question was the research should not be approved by the local IRB if there is not some reasonable prospect of the product becoming available. I would like to know if that stance is realistic. Given, first of all, my own limited, albeit limited experience sitting on an IRB for the last 20 years in which the question has never arisen and, in fact, when we hear from some research that is now sponsored by the National Cancer Institute and the Eastern Cooperative Oncology Group, that as soon as the product is approved, even if the study is

still going on, the sponsor will no longer provide that cancer treatment that they are getting in the thing but it is up to you or your insurance company of all people to provide the product. This is while research is still going on.

So given the fact that this issue has, to my knowledge, rarely, if ever, been raised by IRBs in the U.S. and to expect the researchers in the host -- I mean, the IRB, the research ethics in the host country to reject it, even if otherwise the so-called benefit risk assessment is adequate, does not seem to me to be realistic.

So I would like to hear your response.

DR. DICKENS: Yes. I think it partly goes back to the question raised by Dr. Cassell and my response. It turns on the purpose of the research. If the research is to develop a product for affluent markets, then testing it in an impoverished market would seem to be unethical.

If one has the level of sophistication in the host country's REB that includes a perception of some level of public accountability, then it could be that the host country would find benefits, not of continuing provision of therapy, but other benefits so we may think of them as a spin off benefit that justify their

approval of the proposal.

One of the recommendations in my paper that I did not include in my oral presentation of it, is that U.S. IRBs might ask the host research ethics board to state in writing the benefit they find in the study, and if that benefit is pie in the sky hopes and expectations, then it could be that one thinks this is not the appropriate setting.

If the host research ethics board identifies benefits that are not perceived by the sponsors but are sufficient to satisfy local people, then I think that is an opinion that ought to weigh significantly in the balance.

DR. MACKLIN: Would the spin offs -- I mean, just to follow-up briefly. Spin offs can be health related or they could be not necessarily health related. That is some capacity building might be in -- well, I do not know -- providing the kinds of things --

DR. SHAPIRO: Roads.

DR. MACKLIN: Pardon.

DR. SHAPIRO: Roads.

DR. MACKLIN: Well, roads but -- yes, I wanted to try to find something that would be -- that would fit into what happens when there is training and research is carried out.

So, for example, maybe a laboratory is set up or -- and that is probably close to health related -- or they get a whole bunch of computers because they have to do the data analysis and they get things that are not directly health related.

In other words, how far from the resulting products of the research may these spin offs be, to count in a risk benefit assessment, where traditionally that has been viewed somewhat narrowly? That is risk to the subjects and benefits -- including benefits to others but benefits more directly related to the research?

DR. DICKENS: Yes. I cannot answer that on the substance. My response is one of the process. That is if the local people identify what to them is a justification for introducing the risks to their population then one ought to evaluate that. This is not to say that one wants to risk coercion of high risk studies of no health benefit because of computers or other electronic trinkets. But if there is something of value as identified by local people then I think that is something of which account ought to be taken.

DR. SHAPIRO: The last question, Alta.

PROF. CHARO: I will pass.

DR. SHAPIRO: Thank you very much.

I want everybody around the table to put their electronic trinkets away.

But, in any case, I would suggest that we allow Professor Dickens and ourselves to take maybe a five minute break before we go to looking at the Canadian system because we are running a little behind schedule and we will have to contain the time for our next subject.

(Whereupon, at 9:46 a.m., a break was taken.)

ETHICAL AND POLICY ISSUES IN THE OVERSIGHT OF HUMAN SUBJECTS RESEARCH

DR. SHAPIRO: All right. We are going to change our focus here somewhat. These topics that we are dealing with, the particular reports we are working on, of course, are interrelated to each other so we cannot claim it is a complete change in focus but we do want to move now a little more formally towards our oversight project.

And we want to take advantage of the fact that Professor Dickens is here to talk to us about other approaches to oversight here, particularly looking at the Canadian perspective.

As I mentioned earlier today, you have all received the Tri-Council report, which I think does give a good summary of where things are, at least,

heading in Canada, where the situation is structured somewhat differently than it is in this country.

So let me turn once again the microphone over to Professor Dickens to give at least a few comments of how he sees the structure from that perspective and then we could have questions.

We are going to try to finish this aspect of this morning's discussions around 10:30 so that we can proceed to some of the other issues that are on our agenda.

Professor Dickens?

OTHER APPROACHES TO OVERSIGHT OF HUMAN SUBJECTS RESEARCH: THE CANADIAN PERSPECTIVE

BERNARD M. DICKENS, Ph.D., LL.D.

DR. DICKENS: The initial point is historical. That is the Medical Research Council of Canada had guidelines initially in 1978. They were revised in 1987 and those guidelines worked well enough until the mandate of the Medical Research Council was changed.

It was required to keep all of its clinical involvement but to move closer to public health assessments as well to consider community health. And that meant that it had to expand beyond the model of clinical research into a public health dimension.

That meant that it had to engage disciplines

beyond the medically scientific to consider aspects of social science, psychology, evaluation of satisfaction with programs, and that engaged the areas that formerly had been allocated to other funding councils.

In Canada, there were and for the time being are -- this may well change with consolidation -- but there are at present three federal funding councils. The Medical Research Council, the Social Science and Humanities Research Council, and the Natural Sciences and Engineering Research Council. And all three of them have had interests in health matters.

They are self-evident for the Medical Research Council but the Social Science and Humanities Research Council had been very concerned with issues of resource allocation, consumer satisfaction and consumer access. In addition, the Natural Science and Engineering Research Council had an interest in medically implanted devices but also has funded a lot of psychological research.

And it seemed implausible that there could be a discreet body of medical research ethics, in contrast to social science research ethics and engineering and psychological research ethics. And it was, therefore, concluded that there ought to be unified ethics and a

unified document expressing them.

The document has a title that does not include the word either "code or guidelines," The word "code" cannot be used because when that is translated into French it means a legally enforceable document and this is not directly legally enforceable. Again the word "guidelines" had been used in the past but this invited the comment that guiding is not the same as governing so it left questions of enforceability.

The way the existing code functions then is to attempt to integrate research ethics across a whole spectrum of disciplines not limited to the scientific disciplines. There is little reference in the Tri-Council policy statement to scientific validity. The phrase is "validity according to the discipline." Disciplinary validity because this will include nonscientific disciplines.

The document then is called a "policy statement" because it represents the policy that will be the precondition to funding of research by any of the federal government agencies and it is following the U.S. model. The expectation will be that institutions then available to receive funds will observe the policy statement in all of their research, both funded and -- both governmental funded and funded by other sources

and, indeed, not funded at all such as in the case of student protocols. To that extent then the intention is that this will be the single policy on which research will be conducted.

In addition, I mentioned the three federal funding councils. We also have the National Research Council of Canada and until last summer, I chaired their Research Ethics Board and they, of course, are fully committed to observing the policy statement. Not least because of the political embarrassment of seeming to depart from it.

The merit of the policy then is that it integrates all of the different techniques of health related research across the full spectrum and the federal agencies will expect the policy statement to be observed in all institutions that are capable of being funded for any of their research.

In addition, the private sector does not want to seem to be pursuing lesser standards and in that sense there is a wide recognition that this will be the uniform basis.

With regard to the details, the working group that produced an initial draft that went to the three councils on which I served was very strongly influenced by the U.S. Federal Regulations. In a sense I am not

really presenting anything that is substantively different. If anything, quite the reverse. That is the leadership role of the United States, because of the breadth of its funded research, not just in North America but worldwide, and the commentaries that are the commentaries on monitoring of research in the literature are so strongly influenced by the U.S. Federal Regulations, that this is becoming an international standard and the structure of our Research Ethics Boards very closely parallels the structure of U.S. IRBs.

The enforcement, though, is somewhat different. The Federal Government has a fiscal control in that it can withdraw funding from, and refuse future funding from, institutions that do not conform to the policy statement but legal enforceability is more at the private level. That is, there will be contracts between the federal funding agencies and recipients of their funds and, of course, those contracts will have an explicit term that there will be conformity to the Tri-Council policy statement.

But with regard to otherwise funded and nonfunded studies, the expectation at the university level will be that investigators who are appointed as researchers or the hospital level, the clinicians who

undertake research will do it in conformity to prevailing standards. The policy statement sets those standards. In that sense the legal enforceability would be through private sector relationships rather than through any body of public law.

This opens certain room for negotiation because one often knows that if there are breaches of contracts the result is not the ending of relationships. There will be discussions. There will be undertakings.

There may be some repayment but there will be undertakings of future compliance and the relationship will continue. That is one does not anticipate that it will be a dismissable offense for faculty members of universities to be in breach of the policy statement.

If, of course, there is wilful defiance, then that becomes a more serious matter, but there is more scope for negotiation that characterizes private sector transactions, including so-called alternative dispute resolution. You do not have to rush into court on each of these occasions.

Perhaps I ought to comment on weaknesses of the system. There is the weakness I commented on before the break at the level of monitoring, and although one has the fairly conventional rhetoric now

with regard to vigilance about adverse incidents, we have not yet moved into any structural accommodation of the need for monitoring.

I might point out that the policy statement has been operative only since the end of September of last year, and in that sense we are still in the early days of adjusting to it at my own university, which is a major recipient of federal funds. It is having its own variant, its own implementation of the policy statement approved by its governing board. We hope approved by the governing board on the 18th of this month. So in a sense we are still moving into structural accommodation.

The fact that an independent working board, a working group was established to revise the 1987 MRC guidelines, came about because the National Council, formerly called the National Council for Bioethics in Human Research, was established jointly by the Medical Research Council and the College of Physicians and Surgeons of Canada, and it was their creature, and it seemed improper that that creature of the Medical Research Council should be making guidelines for the two other federal funding councils. So the issue had to be detached from the control of any one of the three agencies.

Now the three federal councils are contributing to the function of the renamed National Council for Ethics in Human Research. The evolution from so-called NBEHR, bioethics, to NCEHR. It is poorly funded and it does not really have the capacity to deal with issues that have already arisen. Again my own university has referred issues to NCEHR for clarification and their response is they have no capacity to respond and in that sense we have a funding and administrative problem.

The expectation of the working group was that this new agency, NCEHR, would become the guardian of the policy statement proposing clarifications, amendment where necessary, and monitoring enforcement. At the moment, we see little capacity in the agency to have any general impact and this is a matter that will require attention.

The last point I will make is that the Medical Research Council itself is in the process of evolution to Canadian Institutes for Health Research, very closely modeled on the description of NIH, that is bringing the different institutes under the same umbrella for administrative purposes. In that sense the influence of U.S. practice has had an impact north of the border.

DR. SHAPIRO: Thank you very much.

Let's see who has questions.

Bernard, let me begin by just asking a clarifying question. Is it the case in Canada that these guidelines or whatever the right term to describe them, are or are not applicable, for example, to private corporations doing human subjects research?

DR. DICKENS: They are not directly applicable. On the other hand the policy statement does address so-called private research ethics boards and the expectation has been -- and this has been reinforced by the pharmaceutical industry itself that it will be in compliance, indeed, because it believes that it is substantively complies with the U.S. guidelines. It believes that it satisfies the evolving Canadian guidelines.

DR. SHAPIRO: One of the things that struck me in reading the document was the attention paid to particular communities and the sensitivity that the guidelines called for in doing research, whether these are various indigenous groups or other communities that might be defined in the Canadian context. Could you comment on how well that has been received? How people think about it? Are people mad about it? Do they like it? What has been the reaction to that aspect of the

Tri-Council?

DR. DICKENS: You are correct in identifying special concerns with the native community, aboriginal groups, as inspiring what appears in the policy statement. The working of the -- or the functioning of the working group was strongly guided in this regard by a member who is an anthropologist who has done research with native communities and a lot of the experience initially came from there.

The working group concluded that we ought to generalize and not target one particular population so we went broader speaking of collectivities. That was a focal point of considerable negative reaction in the research community saying that the definition was so amorphous that it could include a family, genetically linked people, and it was inoperable. So the working group cut back and became more modest.

When the working group submitted its draft to the three councils they tied it back in to an aboriginal context but recognizing that there would be no particular negotiations with the native community. So the issue was one of ongoing contentions and aboriginal groups say they have been -- as one put it -- researched to death and their circumstances have not improved. Again relating to this morning's discussion

about risks and benefits. And the Federal Government has not revisited the issue because of its ongoing sensitivities.

DR. SHAPIRO: Thank you.

Other questions?

Alta?

PROF. CHARO: Bernard, although I know this has been distributed, I must confess I do not have it with me and so I have forgotten some of the details. We have been struggling here with some issues concerning the appropriate scope of U.S. regulation. The first has been on whether the regulations should govern research or they should simply in an almost tonological fashion they should govern that which needs to be governed.

To the extent that they govern "research" there have been struggles over the appropriate definition and whether the definition would include things like oral history projects or polling processes, epidemiological research, surveillance, evaluation programs, monitoring programs, et cetera.

Can you remind me how it is that the Canadians have resolved the question of what the scope ought to be and how to express that in words?

DR. DICKENS: The scope is intended to be --

right, it would include recording oral histories and many of investigators in the humanities were startled to learn that they are now subject to the guidelines and have to get REB approval before they have lunch with people and chat about dead people.

We have a fast track mechanism under which the minimum risk research can be approved very quickly but it is still amenable to independent scrutiny.

The issue in a sense feeds back to a comment in my paper before the break this morning trying to stratify different levels of risk. Risk of physical invasion requires profound scrutiny. Violation of personal identities or confidentiality issues is important but not a physical risk. And speaking to people as part of one's research of nonpublic records can be dealt with in not an entirely summary fashion but without too much agonizing.

PROF. CHARO: And to follow-up precisely on that, you just outlined now a way of dividing up the world of risk by categories, physical versus the nonphysical. As you well know, the American regulations currently do it in terms of “level of risk” with a division at the point of “minimal risk” and a set of words that are supposed to convey the meaning of “minimal risk.”

Does the Canadian system continue -- use that notion of levels of risk and, if so, how does it define that?

DR. DICKENS: No, it does not incorporate that as such, but again the pervasive U.S. influence -- I will not use the expression "the colonizing influence" -- but the pervasive U.S. influence carries across.

PROF. CAPRON: Such a comment would be particularly out of place given the origin of our chair and executive director.

DR. SHAPIRO: Thank you.

Any other questions, Alta?

Are there any other questions people would like to ask?

I have a -- I am just not certain in my own mind just what the enforcement mechanism is. You mentioned, of course, that they would be -- it is a funding tap, which is, of course, the main mechanism we have here. And is there -- and you mentioned that in your own comments. Are there any other mechanisms at all or that is really besides persuasion and moral suasion and so on, is funding mechanism really the issue that holds people's feet to the fire here?

DR. DICKENS: Yes. It is really fiscal control in that there are governmental contracts

between the federal funding agencies and recipient institutions then those that are in breach of the policy statement would be in breach of that contract with all of the contractual remedies. But one also considers the public shame of institutions jealous of their esteem being publicly characterized as violating rules.

DR. SHAPIRO: Thank you.

Any other questions?

Eric, do you have a question? Any other questions?

Alta, excuse me.

PROF. CHARO: Did you want to go first, Eric?

DR. MESLIN: Go ahead.

PROF. CHARO: Since you also rely on the review board process, I was wondering how it is that review boards are recognized as being adequate and if there is any mechanism for ongoing assurance that they are adequate. You are probably aware of the debates now about accreditation of IRBs and even accreditation of investigators. I was wondering what is going on in Canada with regard to this issue.

DR. DICKENS: We are really quite similarly situated. This is an ongoing concern and whether a reinforced national council for ethics in human

research could become a credentialing organization is something that has already been addressed.

There is a certain level of reciprocity in that multi-center studies would be concerned with the caliber of research ethics boards and other institutions. Those that seem to function well and have credible personnel would be accepted in other institutions. Those that are not necessarily worse but are not as well known, not as well credentialed, would be discounted and each institution would then conduct its own process.

At the institutional level discussion in a number of institutions, including my own, has considered something analogous to the process by which faculty members can be appointed to the school of graduate studies and be available to supervise graduates. Whereas novices or recently appointed faculty ranks would not be appointed to a graduate faculty.

One thinks that there might be a similar process of individually credentialed people who would compose committees that would carry weight. That is not to say that one cannot initiate novices into the system but one thinks in terms of the experience, the track record as being important.

It is significant and again I think reflecting the U.S. position that many of the particularly valuable people who serve on IRBs or REBs are themselves investigators.

What we have not yet achieved, and this is an institutional problem, though the three federal councils are concerned about it, is that at the university level individuals who spend time chairing and serving on IRBs get little credit for it. And it is not entirely thankless, but the thanks do not necessarily have a reflection in one's progress through the ranks and that is something one wants to pay attention to.

The hospitals and the medical departments are resistant saying that there is no means of determining excellence in service on an IRB in the same way as one can as an investigator, and that is a problem. All you can do is to check attendance. It is not quite the same.

DR. SHAPIRO: Alex?

PROF. CAPRON: There has been a theme, Bernard, throughout your presentation, which I have found very interesting and provocative, and that has been the emphasis which also appears in the Canadian document on the value of research and, indeed, what is

stated in the document as the fundamental moral commitment to advancing human welfare, knowledge and understanding, and to examine cultural dynamics, which I guess was a bow to the social scientists on the Social Science Council.

And years ago Jay Katz and I began the introduction to his case book on human experimentation with a sentence, which as best I can recall it, says that the human subjects issue, the research issue, raises the question when, if ever, society is justified in exposing certain people to risk for the potential benefit to themselves, to society or to the advancement of knowledge.

And a lot of the emphasis in recent years with the recognition that the exclusion of women from research has disadvantaged women as a whole, and now the recent emphasis on children being therapeutic orphans again, as it were, when drugs have not been tested, and the exposure to children as patients to what amounts to kind of a random experimentation on them as drugs are used which have not been tested. Putting the weight again on the notion of more systematic testing.

I think back to a statement of the British Medical Association, I believe from the 1960's, which

basically said it was unethical to test on unconsenting -- on children who were too young to give consent.

Clearly that view, which is a prohibition drawn out of, I believe, the common law view and widely held among American physicians and American lawyers at the time in the 50's and the 60's that you could not enroll a child who is unable to consent is diametrically opposed then to this more current view.

And the more emphasis that is placed on the current view, and at several points in your comments on international research you emphasized that it was appropriate, in effect, for the leaders of a society to decide that the benefits in terms of capacity building or the like to the society were sufficient that they would approve a research project in our country, either as the Ministry of Health or as the members of an REB, IRB, raises for me again that concern, that balance, that question when is it ever permissible to expose some people to risk because the process, it seems to me, of weighing the benefits to a society as a whole against the risk to a few people inherently has such great weight on the social side.

I mean, if we are talking about the development of a drug that could be good for all children, a vaccine which will then be used as a

standard childhood vaccine on all children and prevent a disease, the weight there in making the risk-benefit ratio is so great.

I wonder whether in the Canadian document, which begins to me so strikingly by the assertion of that fundamental moral commitment to the advancement of knowledge where you get -- where you -- or how you come to a proper recognition that it is going to be a small number of people who are placed in harm's way. Whether it is the physical harm of the medical model or psychological or social harm, and so forth, for that collective benefit and how you can ever expect any process not to weigh more heavily the advantages to science and society over the risks to the few who are in research.

DR. DICKENS: It really goes back to the inspiration of the policy statement and its evolution from the 1987 Medical Research Council guidelines with the obligation to initiate community health studies.

You are right that there are problems in, as you put it, imposing risk. The model, of course, is the voluntary assumption of risk by adequately informed and competent people and the emphasis on disclosure and so-called informed consent you will be very familiar with.

The latitude that one has comes again from U.S. experience monitoring the early effects of the U.S. federal regulations and seeing whether they led to the exceeding of the risks of every day life.

We know that there are risks in every day life quite unrelated to research. The model I take is of the mother with a child attending school who has to be delivered in the morning and fetched in the afternoon because the child cannot navigate dangerous highways alone. There is also a young child of the family. That young child is strapped in the car and is driven through rush hour traffic on perhaps slippery roads to pick up the other child of the family. There are risks of road traffic accidents and the young child will be the victim of them. Those are the risks of every day life.

And if one can have some credible assessment or quantification of those risks then one could take that as a model saying that the risks of every day life are part of growing up in a family and a community and everybody bears them. And if those are not exceeded for the purpose of research that is subject to independent assessment, then those risks can be assumed by parents for their children and imposed on the children.

And if we have systems of public accountability reinforced with public monitoring, we know that public agencies make decisions constantly that are for the health of the body politic, not necessarily the health of the body of each individual member of the body politic.

You have given the example of vaccines, which of course in some countries are mandatory against childhood diseases for children of school age. We know there are risks but the cumulative benefit is taken to justify those risks.

PROF. CAPRON: But it is interesting -- I do not want to extend the discussion of this. It is just to me a reminder that anything we do in this area I think has to quite explicitly talk about that fundamental tension because the researchers -- I think most researchers would object to the notion that the process in which they are engaged should really be analogized to the sort of much more public and politically influenced decision making that says "let's put a road through this neighborhood rather than that neighborhood," and disrupt the life of these people for the collective benefit of having the road as opposed to those people.

And that is the kind of process which -- in

which the considerations that are brought to bear about political influence and so forth would if they were raised in a research study -- well, let's select this group of people to be the subject rather than that, because politically that is where the power lies or whatever, would be regarded as quite foreign to this high minded enterprise on which people are engaged.

So in raising this I am not trying to say that we are in an impossible situation or that there are no ways out. I do not find in the end the analogy -- the argument about informed consent fully satisfactory because we begin this process by saying we are not going to have this be governed solely by the contractual model of informed consent in which two people who are competent can enter into an agreement to do almost anything.

Rather we are going to limit what can be offered and even limit it beyond what a physician bound by his or her own hippocratic duties not to take advantage of a person and so forth might be willing to offer and a patient might be willing to accept. And we say, "Well, we will not let certain things go forward because they are too risky even if there would be patients who would line up as subjects to agree and so forth."

So we are placing limits and the choice of what those limits are and with whom the experiment can go forward. Is this collective choice, but to the extent that it is driven by the notion, “well, it is for the common good that all this is going on, if it were not for the common good there would be no justification for it in a certain way?” I mean, that is -- the benefit side has to be there. Testing something that has no prospect of doing anyone any good would be per se unethical.

But the flip side is, “the greater the common good the greater risk that decisions will be made which could be harmful to some people” and I just think we need to keep that in mind and the contrast between the statement here, which I would take to be the dominant view. I do not think the Canadian view is unusual here. I do not think it is articulated in the same way in the American regulations but I think that it is there. It is certainly there at the NIH which had until now been the repository of the governing body for all this.

Would the view -- the contrast -- would that -- of that view, with the view articulated by Hans Jonas years ago that research is really an optional good, not a mandatory good the way protection of human interest

and human rights is a mandatory good. And we sometimes forget that.

DR. DICKENS: Yes. I think one of the values of a federal document, both in the United States and Canada, is that it does bring to the surface the political context in which knowledge is pursued.

With regard to research being an optional good would it be tolerable to say in the communities that we know and other communities that we have experience of and can imagine that knowledge is now finite? All that will ever be known is known now and there will, therefore, be no further research into pediatric care, geriatric care --

PROF. CAPRON: I think the point of Jonas' statement was to say it is optional in the sense that it ought not to be gained at certain prices and it may well be that had all the slaves not built the pyramids of Egypt we -- Egypt would not have had the glory that it had and we would not look back on Egypt. But whether the existence of those great monuments justified the deaths of all the people involved would -- is a serious problem. And the great monuments -- the advancement of knowledge ought not to be bought at certain costs. And that I think is the point.

So that, yes, if the only way to advance a

particular line of inquiry were to sacrifice the interest and welfare of the society that did that would, I think, in Jonas' argument be a poorer society notwithstanding the greater knowledge of pediatric care that would have come out of it.

I am not arguing against research as such and I do not think he was. I am simply saying that it is a reminder that there may be some things in terms of human dignity and welfare and respect for persons that outweigh the advance of pursuit of knowledge.

DR. DICKENS: Yes. I am certain that is so and one of the functions of IRBs is to determine levels of risk they think it unconscionable to invite people to take and in a medical context one sees those as risks to life itself and future health, capacity to function.

Of course, the other way of looking at the prohibition of unconscionable risk is paternalism or parentalism, guarding people who perhaps are perfectly capable of making their own decisions.

Yes, but I think it is right that IRBs, as Canadian REBs, should say that certain levels of risk simply cannot be imposed or rather cannot be proposed for individuals to assess.

So just to be anecdotal, I recall a study of

meningitis that was suggested to vary standard treatment when parents brought an unconscious child into an emergency department, and the assessment was that it is impossible to ask people in those circumstances to exercise any judgment. They want doctors to do what doctors do for the well-being of their child. And that was not acceptable as research.

The disclosure that enterprises have risks is something that we do accept. You gave the example of building the pyramids.

My brother is in the construction industry, formerly for the Hyatt Hotel company, and although they did not quite build pyramids, they engaged in major construction enterprises in which lives were lost. That is, one would know in advance that a project of this scope has dangers. One has regulations to minimize and hopefully to exclude but one knows that there is always that risk and people with the maximum protection, which is always incomplete, will be equipped to take those risks.

DR. SHAPIRO: Thank you very much. I really want to thank you very much for being here. I found a wonderful phrase in your paper. At least I liked it a lot. You were referring to common law and characterized it as having an enduring capacity to

resolve matters and I hope that is what we can aim for here in our oversight project. At least if we achieved it I would be very grateful and satisfied.

But we are very grateful to you for spending time with us today. Thank you very much for being here.

DR. DICKENS: Thank you. My pleasure.

DISCUSSION WITH COMMISSIONERS

DR. SHAPIRO: And we will move on to the next item on our agenda without a break since we are running a little bit short of time.

Marjorie?

I do want to also ask Arturo in a moment, whenever you are ready, to report on the Orlando meeting.

Do you want to do that first?

DR. SPEERS: Do that first.

DR. SHAPIRO: Okay. As you know, we have been having these town meetings regarding trying to talk with people who have experience in IRBs regarding their experience under the current system, suggestions they might have and so on.

Eric, you can remind me how many of those town meetings we have had already. I think it is four.

DR. MESLIN: Three.

DR. SHAPIRO: Three of them. One was in Orlando and Arturo was down there. That occurred just a few days ago. And so I have asked Arturo just to report briefly on that experience and whether he thought these activities were useful and so on.

Arturo?

DR. BRITO: I will keep it very brief but basically the first thing I want to say is that I found it very useful and I was very impressed with the way Marjorie held or ran the town meeting. I was also very impressed with the people that showed, even though it was a small number of people, with the interest they had and expressing themselves, and giving us some ideas and some of their viewpoints.

And I am going to use my trinket here to guide me a little bit because I do not -- I want to make sure I do not forget some key points that were recurring in the discussion.

Some of these that we have discussed we have discussed before and it is reaffirming to go -- to have gone to this town meeting to hear these again to know that we are not just operating in a vacuum but that we are dealing with what other people really consider.

And then there were some new concepts that were also brought up that I found very interesting and

insightful and I am not sure we want to tackle some of those.

The issue of differentiating between practice and research was brought up and one particular example was given that sometimes research is done apart from the IRB knowing because of the perception of the person doing that research, particularly clinicians, may not perceive it as research but more as a therapy or part of their clinical practice.

The issue of the burden that the IRBs have to bear particularly with assurances and the concern that assurances are more commonly going to community organizations which are nontraditional -- what this -- this is in reference to that more grants are being done in collaborative research with community organizations and the expertise in those areas are probably less than in academic institutions, even though they are usually in collaboration with academic institutions was an area of concern.

And then the emphasis once again on public health research and the current focus of the regulations and how they are based mostly on biomedical research.

One area that kept recurring and recurring is the desire or the wish that the regulations be unified.

Not only the regulation be unified but their interpretation somehow of the rules be unified and make it more standardized.

There were suggestions using templates at different levels. Not just at the informed consent level but, for instance, once again the adverse reporting -- adverse event reporting and making some sort of templates where those could be more regulated and standardized.

The issue of the minority and vulnerable populations was a recurring theme. The -- not just in international research did this come up, but the point was brought up here in this country, particularly with the Indian Health Service and minority populations, and Native Americans that often required tribal consent was an issue, and that is something I really have not heard too much -- at least I cannot recall.

The lack of minority representation of IRBs is another theme that kept coming up and everyone agreed that how to resolve that issue is -- no one had a great suggestion of how to resolve that issue easily but the fact that minorities are often under represented in IRBs was a concern.

The suggestion that the use of research monitor in areas where different communities are

undergoing research was one suggestion.

There was a lot of concern about the fact that the FDA and OPRR have different recommendations or regulations and there was a plea for some sort of a standardization in the one model program. That way it is all -- it is less burdensome for the IRBs to have to decide which falls under FDA, what falls under OPRR regulations or recommendations.

And I think that is about it in terms of the recurring themes that kept coming up unless you have something else to add, Marjorie. I cannot recall anything else.

I just want to suggest that it was really useful for me as a commissioner to attend this and if anyone has the opportunity to do it also to attend it. The hardest thing is not to say too much because you really want to -- the idea is to go there and listen to the attendees and once again it was very reaffirming that a lot of the issues we are dealing with they are concerned.

Oh, the one issue that I had not heard before that was brought up by one of the IRB -- well, it was actually a chair of one of the IRBs from the local schools down there -- is that while IRBs are very careful about coercion as an issue, one of the things

that is not regulated is the advertisers and that in itself can sometimes be coercive in the way the advertisements are made for recruitment for studies. That they, themselves, can be coercive and there is nothing that the IRBs can do about that once they have approved a certain study. So I think that was an interesting point.

DR. MIIKE: It says for recruitment, two nights, $1,000.

PROF. CAPRON: For what?

PROF. CHARO: For what?

DR. MIIKE: It says it was for research.

(Laughter.)

DR. SHAPIRO: Before we go off on that, let's turn to Marjorie and get back to what we have to do today before we leave.

Marjorie?

DR. SPEERS: Thank you.

Just to finish --

DR. SHAPIRO: Thank you, Arturo.

DR. SPEERS: Just to finish up on the town meetings, the next town meeting is scheduled for the day after our San Francisco meeting, which I think is June 7th in Chicago. So it is possible in leaving the San Francisco meeting if you can fly then to Chicago

you are more than welcome to attend that town meeting with us.

We will be getting out to you transcripts from the town meetings because we do take -- we audio tape them so that we can produce transcripts and then we will do summaries of them. So after the June town meeting when we have then done four out of the five that we have planned, we will provide you with the summaries and so you can see some of the reoccurring themes.

We want to spend our time this morning, our remaining time this morning, on the draft recommendation dealing with the definition of human subjects research. I am going to assume that each of you has read the overview memo that I provided as well as the draft recommendation and not go over those but instead suggest that we turn to page 2 under tab 3B and focus as much of our attention as possible on lines one through 22.

On that page, on page 2, beginning with lines one through three, what we offer here is a definition of what a human subject is, and I would like to have some discussion on this particular definition of human subject because it differs. It differs from what is currently in the regulation.

And then to move on to the definition of research that is offered primarily in lines five through nine, and then again the other key point occurs in lines 16 through 22. And I would like to have us focus our discussion on that part of this text initially.

DR. SHAPIRO: Marjorie, just going to the first part of this, the first three lines, which deal with the proposed definition or articulation of what we mean by human subjects, do you want to just take a moment to highlight what you think is the key difference or differences between this and what current regulations say because -- just to make everybody focuses on the issue involved.

DR. SPEERS: Sure. Thank you.

Yes. One -- in the current definition of human subjects, one of the criterion for qualifying as a human subject is that the individual needs to be a living individual. I left out the word living in this definition and so this could include or would include, as it is written now, dead individuals as well as living individuals. So I would like to hear some discussion on whether you do want to broaden it to include dead individuals.

The second part of this definition that I

would like to have some discussion on is the current definition of a human subject includes the words "about whom the investigator conducts the research." So that it includes studies where the data that are collected are collected about those individuals.

Therefore, in studies where individuals are included or involved in the process of the research but information or data are not collected about them, they do not meet the regulatory definition of a human subject and I gave you two examples in the memo.

For example, and I will just go over those. For example, if school officials are interviewed about students in the schools, the students are the human subjects, not the school officials. Likewise in an employment setting it is the same type of thing. If an individual is interviewed about other individuals it is those others who are the subjects, not the ones who are actually interviewed if you take a strict regulatory definition and interpretation of that. And I do have evidence that that is the current interpretation from OPRR of that definition.

PROF. CAPRON: And you have not changed that.

DR. SPEERS: Well, it has only -- what I have done here is --

PROF. CAPRON: Data are collected about --

DR. SPEERS: -- changed it slightly but not enough. You are right. I am not clear on that. And part of it is because I want the discussion -- I wanted the discussion today as to how far you want to go with defining a human subject.

DR. SHAPIRO: Okay. Thank you. That is good. Let's take questions now.

Diane and then Eric.

DR. SCOTT-JONES: I have some questions about the last point that you just made, Marjorie, and I would like you to clarify for me how this would work in certain categories of research that are very, very common in my field.

One is studies of parent-child relations and of adolescent-parent relationships in which the adolescent or child may be asked to report on their interactions with their parents. If you took the definition that you just gave then the parent is the participant in the study and not the child or the adolescent and that is not common practice now. Common practice would be to consider the adolescent the subject even though they are reporting on what their parents do with them and how they relate to their parents.

Another example would be in studies of marital

processes where one person in a couple may be asked to report on the couple's relationship and there are other examples as well. There are studies that are referred to as maternal report where the mother reports on the child's behavior and then the child would be the subject and not the mother.

So I think that would cause a lot of complications in these areas of research and were you intending for that to apply to this kind of research?

DR. SPEERS: What I am intending is to strive for clarification because you gave some very good examples and different IRBs look at them differently. Particularly in the case where mothers give information about their children. Some IRBs will say the children are the subjects and some IRBs will say both the mother and the child are the subjects for it. So it is -- it is open to interpretation because somewhat of -- of what the regulations say and what is good common sense as to who is the subject in it.

The case that you gave where you are looking at diads, so either the adolescent and the parent relationship or marital relationships, that situation is -- depending on how the questions are asked, it could be you are asking questions about the other member of that diad or you are asking about that

relationship. And when it is asking about the relationship it is easier to pull in under the current definition but it still has that same lack of clarity as to who the subjects are.

And, as I say, from a regulatory point of view -- and I really want to differentiate between regulation and common sense or practice, you know, because IRBs can go beyond what is in the -- what is being -- what is in the regulation. But from a regulatory standpoint from what the definition is now of a human subject, if information is not collected about those individuals then they are not considered human subjects.

DR. SCOTT-JONES: Thank you. Let me just give one more example that would be very complicated and that is the study of peer relations. There is a technique commonly used called peer nomination where one child may comment on all of his or her peers in a classroom and they may say who is popular, who is rejected by other children. There is lots and lots of information that one child would give about all the other children. And if you strictly follow that then all those other children, the peers, would be the participants and not the child who is reporting.

DR. SHAPIRO: Eric?

DR. CASSELL: I just -- I looked at this and, you know, it requires some simplification because -- to try and get what is, in fact, the -- what is, in fact, the subject we are talking about.

And it seems to me in taking what Diane just said, that persons are subjects of research whenever data are collected about them, their relationships or activities in a systematic manner in the course of any aspect of scientific investigation. When you go beyond that I do not see how you clarify it. Maybe there is a way to make it clearer after that but I could not see what it is.

PROF. CAPRON: Could Eric just read that one more time for me?

DR. CASSELL: Persons are subjects of research whenever data are collected about them, their relationships or their activities in a systematic manner in the course of any aspect of scientific -- of a scientific investigation.

DR. SPEERS: If you are striving -- I am sorry if I -- if you are striving to broaden it and then this does come down to a scope issue but a simple way to broaden it would simply be to say human subjects are individuals involved in research where data are collected through intervention, interaction or by

access to identifiable private information by the investigators.

If the goal is to capture not only those about whom data are collected but those who are involved in it then you can simply take out the qualifier of about whom.

DR. CASSELL: Well, if you take out that qualifier then the investigator becomes a subject of the research also. I do not think you mean that. Do you?

DR. SPEERS: No, I do not mean to include investigators.

DR. SHAPIRO: Alta?

PROF. CHARO: I am not going to try to wordsmith in this kind of setting because it can be painful in the extreme when we all do it so I want to focus on what your goals are with the language.

And I would like to address your first question about living individuals versus living and dead. There was an article in the <u>New York Times</u> in the last couple of days about people trying to figure out whether Napoleon was poisoned or died by natural causes. If we were to say that we want these kinds of regulations to cover dead people, it would appear that such a study would come under the auspices of federal

regulation.

I understand that it might subsequently be exempted quickly but it would simply mean that the person who undertakes that study would need to present to somebody in order to get that exemption.

I am not yet convinced that we need to do that considering the number of circumstances in which it does not appear that there is any kind of significant societal harm that comes from studying dead individuals, nor are the dead individuals able to appreciate the invasion of their privacy at this point in time. So that the only possible concern would be that as we all go through our lives we will worry that once we are dead our privacy and reputations will be invaded.

If the concern is simply that the study of dead people reveals information about people who are still living, I think a more direct way to get at this is to focus on activities that reveal information about people who are still living and focus on that even if the mechanism is by studying somebody other than the person who is suddenly having information revealed about them.

So we say we are going to be concerned with anybody who is genetic -- whose likelihood of having

the BRCA1 gene is going to be revealed even if that revelation comes through the examination of tissue from an autopsy done on that person's parent.

To me that seems like a more direct way to get at what I think most of the concern is unless there is really a concern here about reputational harm to the dead.

DR. SHAPIRO: Okay.

Alex?

PROF. CAPRON: Well, I actually found the approach that Eric was using responsive to the concerns that Diane had raised. I mean, the question is, is a person a subject when you get information from them or from others about them?

And then I think Alta raised the further question of whether we want to limit the information that creates subjecthood, as it were, in ways that prevents some review process from having to go through an initial examination.

One of the ways of doing that is to put in the language which you had which Eric did not have about private information. That is to say if it turned out that the study of Napoleon was being done entirely from publicly available records you do not have a human subject.

If you are digging into Napoleon's not yet otherwise revealed records held by his family or something or medical records, then whether it is Napoleon or someone who died last week, and you are studying an epidemic and you want to know was the person infected as part of the epidemic, you are dealing with information which is not public, which, therefore, raises the kinds of concerns that might lead to a review.

I guess I am inclined to think that there are going to be gray situations where it is worthwhile having at least the preliminary examination of the proposal by someone who is in a position if there are no risks or if the risks are of the sort that are regarded as not requiring full committee review of saying this is exempted.

But that earlier when we were looking at the regulations the notion that this is a determination which is left to an investigator with no -- with very little guidance and without the kind of experience that an experienced IRB chair or administrator has in the process means that there is the likelihood of mistake in judgments.

Even good faith mistakes (much less people who say, well, I will not submit this and I can later say I

thought it was exempt, putting it in the bad faith) but just good faith mistakes -- is such that I would be inclined, subject to being shown that this is much too burdensome and unnecessary, I would be inclined to say we ought not to build a lot of the exceptions right into the definition but to allow them as part of an exemption or expedition process.

DR. SHAPIRO: Thank you.

Bette? Did you have a comment, Bette?

I am inclined to -- I am sorry, Alta. Excuse me.

PROF. CHARO: No, go ahead. That is all right.

DR. SHAPIRO: I am inclined -- I do not want to get wordsmithed either because that is not productive here but I am inclined to agree that the definition ought to be broaden from where it is now. I am not sure exactly what the best way to do it is and I think Alex is right that we can -- as we go through this we can design a whole set and probably a new set of exemptions so that we do not throw a lot of sand into the mechanism here.

But I mean Napoleon is one example but the BRCA2 example you used I think is the more important one and it may be that it could be built into the

definition. I am not -- I would be quite satisfied if that was the case.

But if someone were to ask me do I think we ought to expand beyond living for purposes of what we are trying, the answer is yes although I do not have the exact way to do it.

PROF. CHARO: Now I would like to take advantage of that opportunity when you called on me before.

DR. SHAPIRO: Yes.

PROF. CHARO: Because I really think that the BRCA1 example that I gave is one that can be handled without having to include the dead as among human subjects because the essence of the problem there is that the work you are doing on a cadaver or on tissues from a cadaver has the potential to reveal information about a currently living individual who is now, in fact, going to be somebody about whom information is revealed.

Although I am not unsympathetic to Alex's concern about reputation and privacy for the dead, I am less concerned about that than I am about, in fact, what I do predict would be an incredibly burdensome increase in the number of protocols that would have to be presented for rapid review and exemption by some

third party.

For example, we worked on the human biological materials report and we saw the scale of activity in that area and since we all started meeting I sent you yet another kind of paradigmatic HBM study on e-mail for you to take a look at.

Now one way in which those studies take place is by using archived samples from the dead and comparing that to the medical records which now give a complete life history of the onset, treatment, course and ultimate outcome.

And that is a very productive and potentially enormous reservoir of research material which currently can be used without any problem and any need to go through review unless, in fact, it is going to be revealing information about current individuals to the point that they become subjects, and in many cases it will not because it is not about particular genes.

It is about infections, for example, or it is about the genetic profile of the tumor and not the genetic susceptibilities of the individual based on some guess about candidate genes for susceptibility to a particular cancer.

I would be loathe to see all that stuff to have to go before anybody for an independent review

before it could proceed.

PROF. CAPRON: Why?

DR. SHAPIRO: Two things --

PROF. CHARO: It is vast. It is vast.

DR. SHAPIRO: Okay. Let me just say two things about that. When we did the HBM report we decided specifically that we were not going to alter regulations. Right? We were going to try to work within existing regulations because we did not want to take that issue on at that time for whatever our complex set of reasons were.

And right now I think we have an opportunity to consider that maybe we want to go with this afresh and really change some of those regulations. Now speaking only for myself, not for Alex or anybody else, but my primary concern is the one you identified. Namely that information gets revealed about living individuals. That is my own primary concern here and I want to get that in, in some way. I do not have a view as to which way it gets in.

The reputational -- the purely reputational aspects of people who are no longer living, I do not find quite -- I will have to think about that first. That was not where my motivation was but maybe someone can raise a good argument for it but I really want to

get the former in, in some way, whatever the right way is.

Alex, did you want to --

PROF. CAPRON: Well, the fact that there will be additional review -- when this entire set of regulations were first being talked about in the 1960's the view of scientists was this will be too burdensome. We now do this work. We are good people. We do this work without all of this requirement. It will be difficult, time consuming, expensive to do it, we should not have to go through it. That in and of itself is not an argument it seems to me particularly when it is stated in terms that are not -- you know, that have not been quantified in any way.

Whether the benefit in any particular case or any category of cases of having a review process that is quick and moves you from category A where you have to go through a full process to category B where you go through a partial process, or category C where you do not have to go through a process at all based upon some scrutiny of what is involved and what the particular risks are. Whether that is worth it or not seems to me to be something which is in principle based upon whether you can imagine in situations like that that there is harm.

PROF. CHARO: Alex, I did not say the argument --

PROF. CAPRON: Let me just finish.

PROF. CHARO: The argument is not that it is simply vast. It was that it is vast and pointless because the only thing it guards against is reputational harm. We can handle the living individuals without including research on the dead.

PROF. CAPRON: Well, there are different kinds of reputational harm though, Alta. There may be very little, if any, reputational harm to finding out whether or not coal miners, indeed, developed a particular tumor at a higher rate than others because of exposure to coal. There may be a great deal of reputational harm to people as to other kinds of revelations from their medical records.

And having some judgment as to whether or not what is involved is a real risk to reputation seems to me no different than the kinds of things we have spent time on in the international area where we have said certain adjustments, certain things could be harmful to people that are not obvious to those of us who are not from that culture. We want to have a process which is capable of taking those things into account and reaching some judgment.

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

Will?

MR. OLDAKER: Yes, I agree with Alta and with Harold, I think, in that if you are going to worry about it, we should worry about how it affects the living.

My biggest worry about enlarging the definition to include the nonliving are basically when you make that big of a jump most of the times there are so many unintended consequences that you cannot even think as to what they are going to -- what you are, in fact, increasing the coverage to be.

And, historically, you know, as Alex knows and others, the law does not recognize the living and the dead in the same way so that, you know, reputational harm such as slander you have when you are alive you do not have when you are dead. I mean, so I would urge us to think very carefully before we cross this line and I right now would be unconvinced that we should.

DR. SHAPIRO: Thank you.

Arturo?

DR. BRITO: Yes. One of the things that I have heard over and over again, including in this town meeting yesterday, is that because of the increased

burden that the IRBs are experiencing with attention to detail and paperwork, et cetera, they do not have enough energy and time to spend on the more important issues. So I can appreciate what Alta is saying and I think that is an important point.

The only question I have, Alta, is if we go your route, basically what you are -- not proposing but what you are expressing here -- my concern about the dead is more from a global level, from the stigmatization level, from the community level, that is where -- and maybe I am a little bit, you know, lost here with this but that somehow be taken care of or how would we take care of that? Would it be through exemptions where this is where -- I just want a little bit of clarification. Have you thought about that? Without increasing the burden to the IRB, how would you --

DR. SHAPIRO: I will let Alta answer in a second. Can I say a word, however, about this issue of increasing burden and IRB work load, which is kind of -- that bar that is raised. Every time you want to think about something you have to sort of deal with IRB work load all over again.

I think that that is an important issue and if we come out of this without any way of relieving some

of the inappropriate kind of regulation that goes on and the inappropriate bureaucracy that we will have failed in our job so we are going to have to develop some set of procedures which helps out on -- we just have to take that for granted and we will get to it when the time -- when the time comes during this process.

But this is not -- this is a solvable problem and I do not want to start off by always having that in front of us as something that prevents us from moving and so -- but we do have to return to it. I mean, it is a very important point. As you pointed out, it comes out all the time, and we do not want to do anything that is pointless, which was Alta's claim a few moments ago, and it might be pointless.

So that -- but let's not get -- let ourselves get stopped every time we think of something but we do have to return to this problem because, as I said already, if we come out of this without any way of relieving some of the concerns we have heard we will really have failed.

Larry and then Eric, and then Marjorie after that, and Diane.

DR. MIIKE: I agree with you because we cannot look at this in isolation. We have got to find ways to

reduce the burden on IRBs and I had suggested something in an e-mail a while back.

I would support this except that I think we should make it explicit we are talking about both living and dead so it should say living and dead in here.

Now the way to address Alta's concern is that if we can carve out an exception where the risk -- whatever you want to call it -- accrues only to the dead individual then that can be an exemption. But I think what we are trying to do is find a way of covering those activities where we have a relational harm and it is -- I think this is elegantly simple and so I would agree with this approach.

DR. SHAPIRO: Eric?

DR. CASSELL: I think maybe we have covered this in the human biological materials report but whatever we do we should be consistent about when we talk about danger to the community and so forth. I think a cadaver is a human biological material and we ought to look and see exactly what we said then and be consistent with that.

DR. SHAPIRO: Diane?

DR. SCOTT-JONES: I just wanted to make a comment about the point that Marjorie made earlier

about those who are doing reporting on another person or not themselves, the participant in the research, but those being reported on are, in fact, the participants. I would like to suggest that we consider some categories different from other categories that might fit that. I have just been thinking a little bit more about it.

When you get ratings of children from teachers or from principals, those ratings are often used along with grades, standardized achievement test scores and so forth as outcome measures of children.

But other categories might be, for example, maternal report, children reporting on parents, where they are involved in that relationship in a different way and there is a different use of the data.

And say in studies of teacher processes or teacher interactions with students you would not typically have the teacher rating all the children so those kinds of studies would not be the ones that would be included. But say where you have teachers rating children or principals rating children and that is used as an outcome measure like a grade or a standardized achievement test score, I think that those might fit very well with what you were talking about.

But those other categories that involve

relationships you might want to distinguish them from that so that they are not all lumped together.

DR. SHAPIRO: I am going to let Marjorie speak. I have to confess I have not thought carefully about a number of the cases. The kind of cases you are bringing up now I have not fully thought out so I do not have any final view in any way on them and I am going to try to think carefully about some of those kinds of cases.

But I have to say just trying to think of the examples that you offered, it seems to me parents of children and children of parents, teacher to peers -- in a research environment now, not in every day life here but in a research environment, it does seem to me that identified information where is related to particular people does make them subjects, whatever we might say about them. That is my initial reaction even though I had not thought about these cases carefully.

And I am thinking of cases where -- which I guess is common in certain areas. We do case reports that appear in the literature, right, of children, parents, husbands, wives. I mean, all kinds of combinations. And it would appear to me to the extent that this was identifiable, at the very least, that everybody in there is a subject regardless of who the

researcher actually spoke to or interviewed or otherwise.

But I really want to think about it more. I mean, mainly I have not thought carefully about it.

DR. SCOTT-JONES: Let me respond. I agree with you that everybody should be included as subjects. I think that Marjorie's point was that the reporter would not be considered the subject but just the person being reported on and I think that is fine in the case of teacher report or principal report of all the group of children. But if you are dealing with say an adolescent reporting on parental relationships, the adolescent is also a subject, so I am agreeing with your point.

DR. SHAPIRO: I understand. Thank you very much. That is helpful.

Marjorie and then Alta.

DR. SPEERS: There might be a way to tie this together and bring us quickly to where we might want to be on this definition of a human subject. One of the themes that I have heard previously from you and I am hearing it today and it is certainly based in our definition of research is that the types of activities that we are talking about have some type of risk or harm inherent in them.

It could be a physical harm but it could be a social, psychological or a dignitary harm. It seems that on this issue of whether to include dead individuals that again that is pivoting around the issue of harm. If there are consequences to living individuals as a result of doing research on dead people then we seem to be more comfortable including that and then it is not pointless. I think that that is right because if something is pointless then it lacks credibility and we do not want it to lack credibility and we would certainly want to have regulated research on dead people when it has some type of a consequence for living individuals.

I think the same principle applies for the other type. A situation of -- if individuals are providing information about others and in providing that information they could incur some risk even though the information is not about them but it could be risky for them then that also should be regulated research. If there is agreement on that I think I actually can write something that says that.

DR. SHAPIRO: Eric wants to make a point in a second but I -- well, Eric, why don't you go ahead before I try to move us on.

DR. CASSELL: That makes a very simple

definition of the subject. A person is a subject of research when they are put at risk by the activity. That makes it very simple.

DR. SHAPIRO: That is a simple thing.

I think what we are hearing, Marjorie, and let's then go on to the next aspect of this, is that there is, I think, widespread agreement that this expansion of the subject -- of the definition of human subject--is a good idea but to focus on harms, if any, to the living.

And I think that both the point that Alta made and the point that Will made was, I think, a very good point, also, which I really had not thought carefully about. And that seems to be what the general sense of this is and we ought to proceed.

Alta, do you want to have the last comment here because I want to get on to the other?

PROF. CHARO: Yes. And it is on this although I have to confess I suspect it might be provocative.

But because you, yourself, said we are in a position where we can rewrite the rules, I think we really need to consider whether we want to continue to include fertilized eggs, zygotes, embryos and fetuses as human subjects.

DR. SHAPIRO: Now why would that raise any

controversy?

(Laughter.)

PROF. CHARO: Since we have the opportunity to write a set of general rules that cover live born individuals and then to have a separate set of special provisions that address the concerns around fertilized eggs, embryos and fetuses, without necessarily having to write the general rules in a way that anticipates those special cases.

DR. SHAPIRO: That is an important issue. We are not going to pursue that right now. We may pursue it in the context of our work but that is really -- I am very glad you raised it actually because we should face it and decide what to do one way or another. And so let's prepare to do that. I am glad you raised it but let's not pursue it right now.

DR. CASSELL: That is opening a can of caviar.

DR. SHAPIRO: That is an interesting metaphor.

(Laughter.)

DR. SHAPIRO: Okay. Marjorie, why don't we go on to the second aspect of this so you can get some feedback on that.

DR. SPEERS: All right. Thank you.

Okay. Now I would like to focus on what we are offering here as a definition of research, of human

subjects research. In this definition we have tried to do two things. One is to remove some of the terms in the current definition that are ambiguous or difficult for researchers and IRBs to interpret. Words like "generalizable knowledge" and the other word -- the other principle word being "designed."

So we have attempted in sentence -- in lines five through nine to improve upon that current definition by providing some clarity. It does not substantively change the definition but I think it gives some clarity.

We have then added in lines 16 through 22 language to incorporate -- to include activities as research activities. These are generally activities that might be activities in the boundary or in the gray area as we have discussed. But to say that activities that involve some type of risk, dignitary, social, physical, economic, psychological, risk to individuals, where these risks are incurred outside of the course of routine practice or procedures.

So in other words, these are activities that would involve risk because the purpose of these activities is what we have given here as the definition of research and that is to collect information, you know, that will contribute to scientific knowledge. So

that we are making a statement here that if you have done them in such a way -- if you are doing them in such a way that it increases risk then for these purposes they are considered research and would be regulated under the federal regulations.

Now we have not said what the regulation will be yet, IRB review exempt or so on, but this pulls them in.

DR. SHAPIRO: Okay.

DR. SPEERS: And I want to say --

DR. SHAPIRO: I am sorry.

DR. SPEERS: -- I think that this definition not only would bring more activities under the regulated set of activities but I also think it does the other, which is there are some things now that are considered research or get reviewed because people do not know if they are research or not, and I think that some of those activities fall out. So I think it goes both ways with potential activities.

DR. SHAPIRO: Thank you.

Diane?

DR. SCOTT-JONES: I have one suggestion for an addition to the set of activities. When we do research with teenagers if we ask any question that has to do with illegal activities, our research is reviewed

differently, so if we ask a teenager whether he or she uses illegal drugs then our research automatically reaches a different level of risk.

So I would suggest that to the set of activities, dignitary, physical, economic, social or psychology harm, that you might want to add "legal" as well because it is very much an issue of concern when we study adolescents.

DR. SHAPIRO: Thank you.

Will, did you have a comment you wanted to make?

MR. OLDAKER: No.

DR. SHAPIRO: Larry, and then Alta.

DR. MIIKE: I am not sure I agree with the last sentence from 16 on in the sense that if we are defining human subjects research I do not see why we need to have in a definition that there are risks in human subjects research. There may be human subjects research that have no risk and those could be expedited or exempted or whatever. But I just find it odd to find the concept of risk in a definition of research.

DR. SHAPIRO: That is an interesting comment. I will come back to that.

Alta?

And then, Marjorie, you may want to just keep

this in mind because we want to get back to the issue that Larry raised.

PROF. CHARO: Yes. And, in fact, I actually endorse it. I understand why we think about that in terms of defining research but I do not think it necessarily belongs here.

I appreciate what this definition is trying to accomplish. I have to confess it did not actually make it easier. It made it harder for me to understand what is supposed to be covered.

And I think part of it is that there is an emphasis on systematic collection and an emphasis on the creation of new knowledge. Now on this latter point I have to got to say that just as a matter of public relations to say that just because you want to do something that creates new knowledge and brings good to the world you are now going to be subject to extra kinds of review may not be the way we want to present ourselves.

But more to the point, for me, the thing that makes research particularly appropriate or regulation is that it is an example of a situation where the primary purpose of an interaction between two people is not to benefit the patient or whatever.

I mean, it is the transformation of a

relationship into one in which although benefit may be predicted in some cases, it is simply not the primary goal. And it is at that point that the person becomes the thing under the microscope, right.

And I would love it if we could capture that relational aspect and not focus entirely on the way in which the information will be used because I think that relational aspect is what gives us the imperative to then say and, therefore, we need some added set of protections for this relationship.

DR. SHAPIRO: I have to think about that. I am not sure. I mean, I think I understand what you are trying to get at, Alta.

PROF. CHARO: It is why -- I mean, it is why, for example, with journalists I do not think we really need -- because, of course -- well, actually -- or polls in some ways would meet everything here. Right? Polling data. So the Harris Poll calls and it would now come under this in many ways.

But there is nothing in that relationship that ever suggested to me any kind of relationship where I would be surprised to know that I am just being used. So one thing I would want to capture is the surprise element when you realize you are being used. I think that is a very big part of the biomedical end of the

research spectrum where you have the problem of the clinical investigator.

DR. MIIKE: Can I just comment on that? I think we are trying to cover too much in a simple phase of the definition. We are trying to cover the whole regulatory apparatus already. And, I mean, the current ones talk about human subject research risk, access, et cetera. I think we should keep -- continue to keep those separate. That is why I had the problem with the latter sentence in this definition.

DR. SHAPIRO: It seems to me the -- I am not trying to focus now on the definition here but it seems to me there -- we have had all this conversation and concern about activities which do involve identifiable information but real individuals and no one is sure if the research -- whether it is screening things or quality assurance or -- and so on, and it seems to me we do need to do something to -- especially when that involves identifiable information to have some protection and oversight in that arena, which is what I think is the aim here. I do not know whether it is achieved but that is the aim.

On polls like the Harris Poll where there is no identifiable information and all you are is a --

PROF. CHARO: It depends.

DR. SHAPIRO: Well, there are all kinds of polls, I understand, and some of them do have, but when they do have and that is a matter of some concern at least for me. When they do not have identifiable information then I do not have any concerns but it is an attempt to try to get at these somehow. Whether it ought to be part of this definition or somewhere else. I have some concerns that we get that activity included.

PROF. CHARO: It is possible though that we could go back -- ratchet it back to a much shorter and more general definition.

DR. SHAPIRO: Sure.

PROF. CHARO: And then follow it with very specific large areas. One area in which people can self-exempt and you might say journalistic --

DR. SHAPIRO: I understand that. Right.

PROF. CHARO: -- you know, Harris Polls. You might want to say market research.

DR. SHAPIRO: Right.

PROF. CHARO: You might not want to say market research. And then another one -- another set where the exemption has to be signed off on by a third party.

DR. SHAPIRO: I completely agree with that.

PROF. CHARO: So that you can -- you can --

DR. SHAPIRO: I completely agree with that.

PROF. CHARO: -- restrict yourself here and then get very specific later.

DR. SHAPIRO: Yes. I completely agree with that. We are going to have to -- as we expand -- especially as we expand the range here, we have to also expand along the lines you have indicated whether it is self-exemption or exemption through one person or whatever it is. I think we do have to worry a lot about that.

Marjorie?

DR. SPEERS: Let me say a couple of things. The text that you have here -- some of this text comes from the current regulation so that, for example, what is in -- on your lines 12 through 16, activities that meet this definition, that actually now comes out of the current regulation. So we are not adding anything.

What I was trying to do with this is to strive for -- strive for a balance between this commission deciding on what should be the scope of regulated research involving humans and having it parallel the regulations that we have now sufficiently so that those who look at this can put it into the context of where

it fits in our system now.

So some of this language was not to pull anything more in. It was simply what is already in the regulations.

The -- I think we have two different points on the table now for discussion. One I think is this issue of knowledge and generalizable knowledge. The -- what I think we do not want to do and what currently does not happen is to regulate, you know, all activities that generate knowledge. There is lots of activities that generate knowledge.

What we are trying to do is to define in some way that kind of knowledge that we are trying to regulate. That I think is the purpose of the term "generalizable knowledge" in the current regulations.

That is a problematic term and so we have here tried to define it differently, maybe not well enough, but again to put some parameters on the kind of knowledge that we are trying to regulate so the emphasis on new knowledge or some of the other words here is getting at this notion.

It is another way of talking about generalizable knowledge so that all activities that generate knowledge are not regulated.

PROF. CHARO: Why would we want to regulate

something that generates generalizable knowledge as opposed to nongeneralizable knowledge? What is the --

DR. CASSELL: Well, one is particular.

PROF. CHARO: I am just -- but I -- but it goes -- it is all circular I understand but why is it that that suddenly gives us the impulse to add new procedures? The fact that it is generalizable knowledge.

DR. SPEERS: I mean, I think that it is what you -- it is the -- it is in a sense the argument that you were making earlier which is that what happens in a research setting is that the relationship between the investigator and the subject changes to -- from one of benefit and interest in the individual per se to an interest in the pursuit of knowledge. And that being knowledge that is of benefit in science which is knowledge then that is generalizable to a variety of situations or to different types of situations.

DR. SHAPIRO: It is knowledge when a doctor makes his patient or her patient better but that is not generalizable knowledge.

PROF. CHARO: But I guess it is just that if the point of saying generalizable knowledge needs to be special -- generating generalizable knowledge needs to be specially regulated, the point is that it is this

kind of activity that, in fact, makes individuals into means rather than ends. Why not talk directly about the concern about situations where individuals are turned into means rather than ends?

It seems to me like we are doing a two step here when we could just go right for the guts of it.

DR. SHAPIRO: Okay. I have got a number who want to make comments. Eric, then Trish, then Larry.

DR. CASSELL: Well, that once again -- we are not interested in regulating the pursuit of generalizable knowledge. We have no interest in astronomy. We are interested in human subjects, where human subjects are concerned. It is what puts human subjects at risk. And then we went on to say the thing we are interested in is a particular thing that puts human subjects at risk, not war or mining or something like that. It is the pursuit of knowledge and in that sense you are absolutely right. It does not have to be generalizable though when knowledge is the primary goal and the person is at -- and a subject is at risk, we are interested. For anything else I do not see what our interest is.

DR. SHAPIRO: Trish?

PROF. BACKLAR: Well, I think that, Alta, you said something extraordinarily important in that we

have never talked about so openly or the regulations do not, that we are using people as means rather than ends. And I think that considering all the discussion and concerns we have had about the therapeutic misconception, it is extremely important somehow to get this right up front and I think that language says it very precisely.

DR. SHAPIRO: Larry?

DR. MIIKE: I think we need to back up about what our initial efforts were, which was what are the areas in which humans are at risk, and we tried to include them, and we really had a list of activities. I would have had a problem with that approach because I think it goes beyond our charge and it is a hard thing to regulate on the human subjects protection.

So we just, by default, had to get back into this by the way in which we define what our jurisdiction is and what the coverage area is in human subjects. That is -- I think that is the difficulty that we are having now.

But the only way that we can do that in replacing the other is to expand the definition and then be very specific about the areas that we exclude or expedite.

DR. SHAPIRO: Other comments or questions?

Diane?

DR. SCOTT-JONES: I have just a fairly minor comment about the second sentence that focuses on what can justifiably be claimed to be true validity and generalizable knowledge.

I think in the way that is written that gets more to the scientific quality than to the ethical quality because generalizability in my view is the goal of scientific research but the way this is stated, it makes these points debatable because research may or may not be justifiably claimed to be true.

The knowledge may or may not actually be generalizable depending on the quality of the study, and validity can always be debated about a piece of scientific research.

So I think the language if this is included would need to be that the goal is generalizable research and not stated so strongly that it occurs.

DR. SHAPIRO: I do not know which parts of this, Marjorie, are in the current regulations or not. I do not know them well enough but actually when I read this I thought that that particular sentence was not necessary. That is either -- it just did not add anything to this and created a problem rather than solved the problem.

So that is just that particular sentence. It does not go to the substance of what we are talking about.

Alta?

PROF. CHARO: Sorry but just because I want to make sure we understand what this as it currently stands would entail, I think the oral history projects about which we heard at the last meeting, which Professor Dickens referred to, in no way do they generate generalizable knowledge. That is not the point of those projects. They are very particularized and so do we want them in or do we want them out.

And I think we can probably come up with a fair number of other kinds of examples in which it is quite specific. A fair amount of qualitative research would be argued by the quantitative ends of the sociology field as being nongeneralizable but certainly involves deep investigation of individuals.

So maybe a more precise list of what we anticipate the definition now includes that is not already included, now excludes that was not clearly excluded, would help us wrap our heads around whether or not we like the consequences of the definition. And that would be a way of testing whether we like the definition itself.

DR. SHAPIRO: I do not know what the other people feel. My -- I mean, that is a good point you make with the oral history. My own view is that it needs to be included. That is just my own view. Whether or not it leads to generalizable knowledge, whatever that means, and I have some trouble with that term also, is -- I guess, it depends, like many other things, on the quality of the study.

If it teaches you nothing and only about that individual, I think it would be a very unusual case. Although there are cases like that. There are cases where they just want to know something about somebody and learn nothing about anything else.

There are cases like that but I think the kind of people we heard from in the oral history area or anthropology area and so on and so forth, I think, in most cases those things ought to be covered. That is that there is significant issues here. It may be that it be very -- you know, very quick review and so on. That is another issue we have to come to. But I really -- my own judgment is that those things ought to be in.

I do not know about this term "generalizable knowledge." I am not going to get stuck on that right now but that is worth thinking about.

Let's see where we are here because I think we

should wind up because we are slowly losing members as the air flight schedules start dictating what we should do. I think we largely agreed, although we have to get the wording right on the human subjects, the area where we are focusing on human subjects.

Now here on the question that once having understood what human subjects are, if we get that then the question is what is human subjects research.

And, in fact, I think, my own view is, Marjorie, for two sentences, that actually can be quite a concise definition if we get the definition of human subjects right. And in some sense that is the more important part of this.

Once we get human subjects right, I think we can get a definition of human subjects research, and there the hard part is to make sure we get the commentary where it belongs and definitions where they belong. I think that is where we really ought to focus some efforts now and try to make the definition of human subjects research really quite concise.

My own view is it could almost be the first sentence here or something like the first sentence and so on. And then we have some commentary on this which helps people understand what it is we have in mind. It might be a useful way to go.

Okay. Any other comments right now? Issues?

Okay. I think we need to talk some but I think we can adjourn the meeting.

Thank you all very much.

(Whereupon, the proceedings were adjourned at 11:40 a.m.)

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