NATIONAL BIOETHICS ADVISORY COMMISSION

HUMAN SUBJECTS SUBCOMMITTEE

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I N D E X

P R O C E E D I N G S

UPDATE AND OVERVIEW

DR. CHILDRESS: Welcome to the NBAC's Human Research Subjects Subcommittee. We are pleased to have all of you with us today as we go through a fairly long and I think important agenda.

Before we talk about what we are going to do today Dr. Harold Shapiro, Chair of the National Bioethics Advisory Commission, will talk about some general NBAC business.

DR. SHAPIRO: Thank you very much and let me extend my own welcome to everyone who is here with us today and to also my fellow commission members, most of whom I have not seen over the summer. It is really good to see you again. I was just saying to Alta just a short while ago I really missed everybody after the long series of meetings. I felt something missing in my life not seeing you all on a more regular basis but we have a heavy agenda this coming year so that should be resolved very shortly beginning today.

The general business and situation of the commission, I think, continues to be in very good shape. We are near appointing a permanent executive director and you will hear more about that in the subsequent days, the next week or the week after that, and that will be an important milestone for us.

Also I hope everyone has looked at what we passed out, a review of our colleague Eric's book which I congratulate him and look forward to reading it. I have not yet had a chance to read it but I intend to do so.

Today's meeting of this subcommittee are really quite important since we are hoping, as Jim will be telling you shortly, to at least issue one report from this subcommittee late this calendar year and that we will have to see as a result of today's meeting if that is a reality or whether we want to do it somewhat later than that.

I am preparing a report of the commission's first year which I will be circulating to commission members within the next three to four weeks for your comments. I hope to issue that some time in November perhaps. It just tries to give a flavor of the committee's work and our future agenda as it is unfolding. So you should all receive an initial draft of that really quite shortly in the next few weeks or so.

Finally, we do have to begin thinking through the evolution of our agenda properly. We are all very busy with our ongoing projects right now and they will not be resolved probably through the middle of next year. Resolved in the sense of resulting in a report on this issues. However, it is not too early to begin thinking about the next items on our agenda.

As you all know, we have many candidates that are being pressed upon us and others which we might feel pretty strongly about. So you will all receive a communication from me also in the

next couple of weeks asking you to think about that and see what kinds of ideas you have. That I look at as really our next important item of business in selecting our next agenda items. Our first few agenda items so to speak have been provided for us either by the President's Executive Order or by events that transpired in the word of bioethics and so on but now we have an opportunity to think carefully about crafting our own agenda and that is a very important item of business which I would like to turn to in the next few weeks. So if you could begin thinking about that and noting down things that you are concerned about that would be extremely helpful.

So I look forward to today's meeting. I know there is going to be some conflict for some of you as we get to 3:00 o'clock this afternoon. You may want to attend two meetings at once. That is not yet quite possible but who knows. Science continues to develop. But this afternoon you will have to make up your own minds on that.

I also want to apologize, especially to the members of the Genetics Subcommittee, that I, myself, will not be here tomorrow morning but that I am sure Professor Murray will carry on that committee's work very effectively.

So, Jim, thank you very much for these few moments. I look forward to today's meeting.

DR. CHILDRESS: Thank you, Harold.

The agenda is a full one. We will start in just a moment with a presentation by Dr. Robert Temple and discussion with him on the importance of placebo-controlled or other difference-showing trials.

After that discussion we will spend the rest of the morning hearing public testimony on the issue of research involving cognitively impaired or decision impaired subjects. A topic that we have already addressed in different ways with the presentations by researchers, by contractors, and by other people who have thought about this area.

Since we hope to move forward in drafting a report and recommendations in this area we thought we could not do so without a more systematic public hearing and thus we will spend this morning doing that.

Then we will turn this afternoon to our own sustained discussion of the kinds of issues involved with particular reference to the way Dr. Moreno identified the issues, the way Rebecca Dresser identified the issues, to try to determine where we want to go in the report. This will be the first chance for us to really spend some time thinking about what we believe might be important directions.

We had thought at one point about trying to have this report done in late November. There is a good reason for not shooting for that date but trying to move along as speedily as we can. The National Institute of Mental Health, and Dr. Rex Cowdry is

here, will be sponsoring a conference on December the 2nd and 3rd, and I will pass out later this morning or this afternoon when we turn to our discussion the schedule for the two days on December the 2nd and the 3rd.

At this point there is a scheduled meeting of NBAC on December the 1st and then this meeting will be on December 2nd and 3rd so we will talk further with Harold about the scheduling that might be possible for several of us to be available for that.

Dr.Cowdry, would you like to say something about that conference at this point?

DR. Cowdry: Sure. The approach that we have taken to this is try to address the issues that were raised in the regulations that were directed at this population in a nonregulatory way building on the IRB structure and trying to provide a bit more structured guidance if you will to IRB members who are required by the current regulations to address whether special protections are needed for individuals who may have some degree of cognitive impairment.

The structure of it will be somewhat similar to a consensus conference in that materials will go out to a group of panel members who represent an array of disciplines, many of whom have experience serving on an IRB, which we felt was important to the perspective of this.

Then at the close of the meeting we will develop a series of, if you will, suggestions about best or alternative practices, of ways that IRBs can fulfill their responsibility looking at the ethical and practical issues of assessing capacity to consent on the one hand and, secondly, whether there are ways of improving a participant's understanding of the research. And then, thirdly, some potential conflict of interest issues that arise in the context of this research.

We considered a fourth issue and decided that the best approach to that is through a different route, namely the issues of research design which have been somewhat controversial. Particularly the use of placebo controls in some kinds of trials. We actually believe that is an issue that we need to address in a different way together with the FDA because so much of those issues are intimately tied up with the drug approval process.

So we look forward to a stimulating couple of days. We hope that out of that will come a series of ways in which the IRBs can fulfill their obligations under the current regulations and we will be delighted to hear from you all. We will have also an opportunity for public comment early on in the process to provide that kind of input into the panel members' deliberations.

DR. CHILDRESS: Good. Thank you.

Any questions for Dr. Cowdry?

Did everyone get a copy of the schedule, I guess, passed around?

Thank you very much. We look forward to that.

DR. Cowdry: Thank you.

DR. CHILDRESS: So that could provide an important context for finishing our deliberations so that may suggest an opportunity for the first of the year for a report and recommendations from our subcommittee and from NBAC.

Then the one mandated task we have is to make a report on the federal agency protection of human subjects, including but not limited to compliance with the "Common Rule" and we have been very fortunate to have had Bill Freeman, Joe Mangel and Emily Feinstein, joined in the writing by Susan Katz and also in some of the interviews by Jonathan Moreno, working on this report and the draft has been circulated and we will talk about that this afternoon. So we are very pleased with the kind of progress our staff has made on this with input from NBAC and we look forward to a discussion of that later today.

So that is our plan for today. We have other things on our long-term agenda and short-term agenda. Harold mentioned the need for us to set some priorities but let me just mention some of the things we have that we can talk about later today as to whether these would be topics we would talk about in October.

We have now received Celia Fischer's fine paper on relational ethics and putting vulnerability in that context. We are in discussion with a person about a contract paper on community that would be important for flushing this out. And with another philosopher for a philosophical analysis of vulnerability. So we have that range of issues to look at.

We, also, last time agreed to spend some time looking at the placement of OPRR and two contracts have been awarded.

That is definite now, is that right?

Ms. Hyatt-Knorr: They are going to be awarded.

DR. CHILDRESS: They are going to be awarded. I am sorry. They are going to be awarded on pro and con and we still trying to find someone who would do a discussion of the possible role of OPRR and dealing with private funded research.

A third topic is international research. This was raised at the last meeting. We sketched a kind of procedure for further discussion of this. The <u>New England Journal of Medicine</u> today has an extended discussion of this topic. Several have thought that it might quite appropriate to spend a fair amount of time at the October 19th meeting dealing with this and we can talk later today about how to proceed, whether even though it would be only a month away we might be get some contract thought papers that could help guide us.

Another topic working is an assessment of the very important front line mechanism of IRB's. We indicated last time that we thought it would be important to get at least the preliminary results of the "A" study and the Office of the Inspector General study. Preliminary results should be available by the end of the year. We need to look at those and then determine what else

we need to do in order to make an assessment of this mechanism that is so important for protection of human subjects and for facilitating research.

So those are at least some of the things that we have to look at and we will come back this afternoon and we will talk about sort of how to proceed but I wanted to at least get those things out before us this morning.

Any comments or questions now before we turn to Dr. Temple?

All right. I am very pleased to have with us Dr. Robert Temple, who is Associate Director for Medical Policy at the Center for Drug Evaluation and Research at the FDA.

Dr. Temple, thank you very much for joining us today.

THE IMPORTANCE OF PLACEBO-CONTROLLED (OR OTHER DIFFERENCE-SHOWING) TRIALS

DR. TEMPLE: Good morning, everybody.

(Slide.)

That is sort of an alternative title from another talk but what I am going to be talking about today, and it is a pleasure to be here to do that, is some of the ethical and practical considerations in the use of placebo controls. As my title I gave you indicated it is not so much placebos, it is the difference between trials that show a difference between the two treatments and trials that in some way do not show a difference but rely on a showing of equivalents.

(Slide.)

The major topics I am going to talk about is FDA responsibilities very briefly, some of the ethical issues and concerns related to the use of placebos, what the need for placebo or other different showing trials is, that is why is this even an issue, and what the problems are with the alternative design that many would propose, that is an active control equivalence trial.

Finally, to the extent there is time, I will try to talk about designs of placebo control trials that can void some of the ethical and practical problems that allow you to use a trial that has a different showing design but that makes for a more comfortable sort of trial design and minimizes placebo exposure and so on.

And then finally talk about how equivalence trials can be supported because there are a number of important situations in which equivalence trials are, in fact, the norm.

Just before I get to that the major pertinent responsibilities of the Food and Drug Administration that relate to this discussion are that we are obliged to determine that a drug is effective for its stated uses before we approve it for marketing. One of our major responsibilities in explaining how to do that the law requires that this showing of effectiveness be based on adequate and well-controlled studies and in regulations describing those studies we identify five different kinds of control groups that could be used in those well-controlled studies.

(Slide.)

Placebo, no treatment, which is similar to, you know, giving people an inactive substance. A dose response study, an active control study and a historically control study. People are often skeptical about historically control trials and those are sometimes called uncontrolled trials but we recognize the possibility that there are circumstances in which historically control trials can be persuasive.

In addition to having to decide on whether a drug can be marketed or not we also monitor the process of drug study, the investigational process, under what are called IND's. We focus principally on subject safety during that period of time. Trials that are carried out should not expose patients to undue risks. They should have appropriate monitoring. They have to involve informed consent and approval by an institutional review board. We will stop a study if it places at people at inappropriate risk and also in some cases if it is inadequately designed to do its job.

(Slide.)

Now the ethical issue with placebos is this, the principle ethical issue anyway: If there is a known effective therapy for a condition is it ethical to deny this treatment to some patients in a clinical trial, which of course you do if you randomize some of them to a placebo. This concern probably exists apart from the Declaration of Helsinki but it certainly is supported in some people's view by a phrase in the Declaration of Helsinki that was added in 1975 that says in any medical study every patient, including those of a control group, if any, should be assured the best proven diagnostic and therapeutic method.

The question that arises at least in our view is doesn't it matter what condition you are talking about?

(Slide.)

Now some people, notably Ken Rothman and Karen Michaels in the New England Journal in 1974 argued that the Declaration has to be read literally and if you read it literally the condition being treated does not matter at all. That if there is a known effective therapy you simply must give it to everyone in the trial.

Now you will probably find these examples self-serving and I acknowledge that but that means you cannot do placebo control trials of hair loss because Rogaine exists and it is effective. You cannot do placebo control trials of antihistamines in seasonal allergy because after all we have effective antihistamines. You cannot study headache, you cannot study insomnia, anxiety, outpatient depression, obsessive compulsive disease, those are probably more potentially controversial, but basically you cannot study anything if there is an existing therapy.

It is worth noting that if you read the Declaration of Helsinki literally you cannot do active control trials either because the people getting the new drug are not getting the best available known therapy. In a sense you cannot even do a

historically control trial because again the people are not getting the best available therapy.

(Slide.)

You can probably tell what I believe from my examples but what E-10 refers is the International Conference of Harmonization Document that is under development. I would say what we have long said and believed is that if you -- we do not think the Declaration of Helsinki meant what Dr. Rothman thinks it meant. The change in 1975 did not come advertised as we think there are too many placebo control trials and we want to stop them. It was intended to remind physicians that there is a patient in this trial and that they owe them appropriate attention, which is a point one could hardly disagree with.

But it has been our conclusion and this is reaching a certain degree of international acceptance that with informed consent and appropriate review by an IRB patients can be asked to participate in placebo control trials even if there is existing therapy when the risk of a lack of treatment is only discomfort. You cannot ask a patient to sacrifice his life by avoiding known treatment. That is an entirely different matter. Or his health, you cannot expose them to irreversible damage. But you can ask them to participate if a discomfort of some kind is the worse thing that can happen to them.

Obviously patients in a trial have to be made fully aware that they can leave the trial. They have to be told that there is existing therapy. All of those things are sort of obvious.

It is, therefore, our belief that at least most psychiatric conditions, outpatient depression, obsessive compulsive disease, panic disorder, anxiety and so on can be studied in placebo control trials. Angina pectoris can be studied in placebo control trials. We actually have a large metaanalysis of all the placebo control trials done some years ago that show no harm came to people who were randomized to placebo. They actually had fewer side effects.

(Slide.)

Now there are a number of situations, including important ones, where one would like to develop new therapies where you simply cannot carry out a placebo control trial. You cannot do post infarction trials of thrombolytics or beta blockers or aspirin or ACE inhibitors at least in people with ventricular dysfunction because all of those treatments have been shown to improve survival or prevent new heart attacks. You cannot ask people not to take that therapy. You cannot forego antibiotic prophylaxis in dirty surgery. You cannot treat leukemics or testicular cancer. You cannot leave at least moderate to severe hypertensives untreated.

By now with the progress of treatment of congestive heart failure with ACE inhibitors almost any degree of heart failure probably needs to be treated. At least you would not want to defer treatment for more than a very short period.

But it is also true for reasons I will explain that doing an equivalence trial in these settings may not be informative so we are sort of as a community kind of stuck. You cannot do the trials and there is not any good way to get the data or at least there does not seem to be.

(Slide.)

Our response I would say to the Rothman formulation is that whether a placebo control trial can be carried out is a matter of some degree of judgment. You cannot expose people to harm but you can ask them to accept discomfort. There are a number of situations in which people could have an honest debate about whether it is normally the treatment that prevents harm and different communities reach different conclusions.

The treatment of most solid tumors is not very effective. In this country we treat them nonetheless as a rule because you can shrink the tumor briefly in many cases. In much of Europe those treatments are foregone. So the attitude toward how to do a trial of a new antitumor agent could be different depending on which side of the Atlantic you are on because there is a different view of the degree of effectiveness.

As you already know there is considerable discussion of schizophrenia. People have a debate about use of a placebo in mild hypertension and it might well depend on the duration of the trial. I do not think people would feel unhappy about a four week trial but as the trial got longer they would.

There has been a debate about whether it is essential to treat patients with antiemetics in severely emetigenic cancer chemotherapy. That seems like a legitimate discussion. That actually is one area where you probably could learn from an active control trial.

Can you use thrombolytics? Can you use a placebo controlled trial of thrombolytics after 12 hours? The beneficial effects of thrombolytics after 12 hours are not well described. There are risks of thrombolytics. Some people would say we really do not know the answer yet. Other people would say the evidence prior to 12 hours really makes that an uncomfortable study. Some people that aspirin has been shown to provide primary prevention of heart attacks. We on the whole do not think so and the people who carried out the major study do not think so but there are others who might disagree. So these are all areas where it is a matter of judgment.

(Slide.)

Let me turn now to why it matters at all. If you could just carry out an active control trial to show that one drug is indistinguishable from another and conclude that the new drug works just as well as the previous drug and that it is effective we would not have a problem with that. If that was a satisfactory approach the issue would not be discussed because other things being equal you would probably rather give everybody therapy.

The trouble is, as I will explain, that trials that do not show a difference between therapies are often difficult to interpret. Again it is not placebos that are so much the issue. It is the showing of a difference. A dose response study with a positive slope is a perfectly interpretable trial. Being superior to an active therapy is always interpretable. It is the ability to show a difference between treatments that is critical.

(Slide.)

Studies that are designed to show equivalence have three principle problems. The first two are the most important. The third can be overcome. One is the historical assumption, that is an assumption has to be derived from outside the study, that the trial had assay sensitivity and I will explain what I mean by that in a moment.

Second, there is a lack of incentives to carry out an excellent study which is a potential problem.

Third, there is not any theoretical or actual way to say what a statistically significant similarity is. You have to define it anew for each study and the result is that the trials get to be quite large and there is some uncertainty about it but one could overcome that if that was the only problem.

(Slide.)

Now the most important problem with a historically controlled trial is that you have to make a critical assumption and that assumption is that had there been a placebo in that trial the control drug that you are using, the drug that you think is active, would have been shown superior to it. In other words, this was a trial that can distinguish active from inactive drugs. Now that might seem like a question one should never ask. We are talking about drugs that are known to be effective. But the fact is that effective drugs are not effective every time we study them for reasons that you often cannot put your finger on. I will give you a lot of examples of how that happens showing that that is the case.

So you have to bring external information to bear on the study to interpret it. In other words, if you see that there is no difference of a certain size between two drugs in an active control trial you have to be able to say, "Well, this trial could have distinguished a difference of X or Y and did not, therefore, I am confident that I must have shown the drug is effective." But you have to be able to say with some assurance that the drug would have, in fact, distinguished a difference of a certain kind. A quick way of saying that is that it would have beaten the placebo had a placebo been there.

What this means is that every active control trial has elements of a historically control trial. As I will say, sometimes this is obvious. You can tell the difference between an active drug and a placebo in treating urinary tract infections. Urinary tract infections do not disappear in five days by themselves for the most part. That is not hard. Tumors do not shrink by themselves, at

least hardly ever. And you can understand what the active drug did in that case.

But if you are treating something with a variable course that has a big placebo response it may be very hard to tell.

(Slide.)

Now this is not a new observation. It has been known for a long time by people who deal with diseases that are self-limited and variable and resolved. So I more or less like to quote a well-known analgesiologist. The title is because he was in the room and I was sort of slightly teasing him. This is Lou Lasagna who has been in the clinical trials business for a very long time.

What he says is that in medical situations that are not critical one can -- sorry. He is saying, "In certain situations you may not be able to use placebo and you can justify a comparison between a new drug and standard even if you do not think you could use a placebo." But that sort of trial is convincing only when the new remedy is superior to the standard treatment.

If it is inferior or even indistinguishable you cannot really interpret the results because in the absence of a placebo you do not know if the inferior new medicine has any efficacy at all and equivalent performance may reflect simply a patient population that cannot distinguish between two active treatments that differ even a lot or, in fact, between active drugs and placebo.

(Slide.)

Certain clinical conditions such as serious depressive states are notoriously difficult to evaluate because of the delay in drug effects and the high rate of spontaneous improvement. Even known remedies are not readily distinguishable from placebo in control trials. How much solace can one derive from a trial shows no difference between a new putative antidepressant and a standard tricyclic. A very compact and efficient way to do it.

What I wanted to illustrate for a while and I will try to be conscious of time and not show all of them in detail are how right Dr. Lasagna was.

(Slide.)

Anyway because of this concern we have actually noted in regulations that if the goal was to show that no difference between treatments is informative you have to give us some reason to believe that trial could have distinguished active drug from placebo. So this has been recognized since 1985.

(Slide.)

The general problem is recognized all over the world. Current guidance for antidepressant drugs and antipsychotic drugs out of Europe reflects the same concern with the need to use placebos.

(Slide.)

What this is, is a slide showing the results of six studies in depression. The trials -- the measurement I am showing is the HAM-D score, a standard measure of impression. And in these

trials they have been used as a common baseline. That is not critical to this discussion.

All three trials used a new drug called Nomaphasine which is no longer on the market because it is toxic but it is an effective antidepressant. Imipramine, a standard antidepressant. And what I am showing you is just the comparison of the two drugs. Now all of these six trials included a third arm. They also had a placebo but I am not showing you that yet.

What I want to show you is that in each of the trials there was a nice fall on therapy at four weeks from baseline to a much lower value, a change of about ten points on the HAM-D score. That is fairly typical for trials. And that the new drug and Imipramine are almost identical in every case.

So you would interpret these trials as showing that the two treatments are equivalent and if you believe that was meaningful you would say, oh, this drug must work.

(Slide.)

I have now added in the placebo group. What you can see is that for five out of the six trials there is basically no difference. Some of them lean slightly in favor of drugs and some of them lean slightly in favor of placebo. There is no difference between the active drugs and the placebo except in one tiny trial. With only seven patients per group, far too small for anybody -- no one would design a trial that way today but that trial was easily able to distinguish the placebo which had very little effect from the two active drugs and the other two did not show anything which tells you that equivalence is not very informative.

(Slide.)

I think I do not have time to go through all of the examples. These are trials of Nefazadone, a more recent drug. The trials are considerably larger. They are 40 and 80. And what you see is a pattern in which sometimes you can show an effect and sometimes you cannot. 4A and B were identical trials. This is Nefazadone, 600 mgs. 300 probably is a borderline dose. But 600 mgs in this trial produces a change almost identical to placebo. In this trial it produces a change that is considerably larger and that is significant. None of the effects are very huge which is worth noting.

In this trial, 002, Imipramine, that is a standard comparison agent, is more effective than placebo. The effect is fairly small. That is worth noting but the trial is big so we have managed to show it.

(Slide.)

In other trials, 006-1 and 006-2, are essentially identical trials. Imipramine cannot be distinguished from placebo. In this trial it easily can and so on. I will not dwell on that.

What I did do was look at about the last three years of psychotropic drug trials and what I have -- sorry for my lack of coordination -- and tried to show the failure rate for trials. So

this is the condition. These are the drugs. This is the approximate size per group in the trials. And these are the failure rates. So for Venlafaxine slow release, one out of three trials could not distinguish drug from placebo. For Mirtazipine, a drug we certainly think works, five out of the ten could not distinguish. And the active control, Trazadone, could not distinguish. But all of the amitrypyline trials in this case were effective. I showed you Nefazadone.

For Bupropion slow release, a dose that is at the low end of 300 mgs, one we certainly thinks work, none of three trials were able to show that the drug worked even though there were 100 to 150 patients per group. Those were huge depression trials but they were not able to show anything. I should say we approved it anyway because it gave blood levels similar to the immediate release and we thought it worked.

(Slide.)

In psychosis we have looked at three drugs recently. Quetiapine, Olanzapine and Sertindole. Quetiapine is not approved yet but it has gotten a statement that it is approvable. One out of two trials of a dose that we are quite sure with a sample size of 200 patients, it is a huge trial, was unable to distinguish the effectiveness of a regimen that worked in many other trials.

Olanzapine, one out of three trials failed. One out of two trials with Halparinole with a group size of about 50 failed. Sertindole, one out of four trials failed.

It is hard to know whether you could define a sample size that would assure you that they would always work but what you can say is that nobody has done it yet.

In obsessive compulsive disease one out of four trials with Sertraline and one out of three with Paroxetine failed. Clomipramine, however, was positive in both of those trials. These are quite large trials, 85 people per group.

(Slide.)

Well, let me move on. This is not a factor only in psychotropic drugs. This is one of two large heart failure trials with Enalapril. There seemed little doubt that Enalapril and other ACE inhibitors are effective in treating the symptoms and also the survival consequences of heart failure. A European trial showed a clear drug effect.

The domestic trial, however, looking at exercise duration, which was the primary measurement, showed essentially the same effect in both cases. If you tried to look at only sick people you got a better trend but it was still not significant because the sample size was reduced. There were two different ways of measuring ejection fraction, one looked good and one did not.

Why this came out this way I have no idea. It looked like a perfectly excellent trial but that is how it came out.

(Slide.)

In getting ready for a recent consideration of a beta

blocker called Carvalol, which failed to show improvement on exercise in all of the three large trials that looked at that endpoint, although they had succeeded in a small 50 patient per group trial, Milton Packer, who is the head of cardiology and cardiology research at Columbia reviewed based on FDA reviews the results of studies of heart failure for four ACE inhibitors and one other drug. He only looked at parallel placebo control trials.

What he found was that on any measurement you could name the trials were highly inconsistent even though we know these drugs do, in fact, work because of the overall database. On exercise tolerance, and the drugs are not named, but one out of two, one out of two, one out of three, two out of four, two out of three showed -- these are the ones that were successful so these are successful drugs.

For symptoms they did on the whole better but not all that good and on symptoms the trials failed. If you look at New York Heart Association classification or global evaluations they, too, were inconsistent. This again is for a class of drugs that we all believe on the basis of well controlled studies works.

DR. CHILDRESS: Dr. Temple, we will have to move along faster because we only set aside 30 minutes and I think we are up about over 20 now for your presentation. So if you could move through and get them to the larger argument you were making so we will have a chance to raise some questions that would be helpful.

DR. TEMPLE: Okay. Well, I am distressed by that. You are hearing my larger argument. The same examples are in --

DR. CHILDRESS: Fewer illustrations then I guess.

DR. TEMPLE: Okay. That is fine.

Anyway if you cannot be quite sure that the positive control would have been effective in a trial you cannot make the crucial assumption that you need to make.

(Slide.)

There is a second problem, I will just go over this briefly, when you are trying to show a difference between therapies your behavior as an investigator or as a designer of trials is all designed to make it as certain as possible you can show a difference. So you assure good compliance and you make sure the people have the disease. You exclude people who have rapid major placebo responses because everything you are doing is designed to make sure that you can show the difference. I mean, you do not want variability. Your behavior from our point of view is sort of automatically excellent.

And all of these examples that I showed you of failures to show difference in drug and placebo arose when people were trying as hard as they could. I think it is fairly obviously that if they have little incentive to do that, and you could if you were cynical say they have no incentive at all, you could worry that the trials will not even be as good as that when the goal is to show no difference between treatments.

(Slide.)

I think I will not get into this but if you try to design these trials so that they are credible and so that they show that the two drugs are very close to each other you end up with very large sample sizes. Now that is not a problem and it may be easier to recruit people for an active control trial so I will not dwell on that.

(Slide.)

I will go through these very quickly. I will just mention them and you can ask me about them later. Even if it is ethical to do a trial that deprives people of therapy that is available that does not mean that they want to enter it and it does not mean that physicians want to enter into it even if it is ethical. So it is worth thinking about trial designs that can allow you to show a difference between treatments but that make people more comfortable or in some cases resolve the ethical problem.

What these are, just a few of them, one is an add-on trial. In heart failure nowadays, for example, you cannot deny people ACE inhibitor treatment but if you have another drug you could add it to that treatment and compare it to placebo as an addition to other therapy. Everybody gets what is known and you still show a difference between trials. That is how antiepileptic drugs are developed now. You do not deprive people of antiepileptic therapy, you add to the situation that is there and compare it.

(Slide.)

It is always good to beat the standard therapy. The GUSTO study showed how that was done. You could do that with Omeprazole. You can beat standard therapy showing the dose response is good but you cannot be cynical and use an inadequate dose on purpose. It is only reasonable to do dose response when there is a reason to want to know the dose response. You can study a subset of a population not known to benefit from the standard therapy because then you are not depriving them of anything that would do them any good.

(Slide.)

I want to mention early escape and randomized withdrawal studies. Just briefly these are situations where you minimize the duration of exposure to placebo. In an early escape study, say in depression, that would mean that as soon as a person failed to improve after three weeks they would leave the study as a failure and you would count failures. That would mean that you would not have to wait the whole six weeks. You have learned that the drug was not working in a reasonable time. Of course, three weeks has to be long enough to test the therapy or you have obliterated your chance of showing anything.

Another kind of trial closely related to that is randomized withdrawal study. In this sort of trial you put everybody on therapy and you make observations and try your best clinically without a control group to say, yes, this antidepressant

worked in that person. You then after a period of time, one that relates to how long you are interested in showing the effectiveness of the trial, you randomly assign people to taking the therapy away and continuing the therapy.

This can be used with an early escape mechanism so that as soon as a person deteriorates to a degree that you consider meaningful but not necessarily as far as they are eventually going to deteriorate they are out of the study as a failure.

That is a very good way -- that is actually how maintenance therapy in depression is studied all the time now and again you can minimize the duration of time that a person is receiving a therapy that is not working for them. You still have to have some period but as soon as that happens the patient leaves the trial and you do not have to wait the whole six weeks.

(Slide.)

If you wanted to make the argument that an active control trial is credible the four things one has to do is show that placebo control trials regularly allow you to distinguish the drug from placebo and try to use a design that is as close to that study as possible. There has to be some estimate of the size of the effect that one could distinguish or the difference between the two treatments that would be considered too large to still be constant with the idea that the new drug works. These are hard things to do.

I can go into that more but there is actually an international guideline being worked out to describe how to do these things and of course a certain degree of redundancy provides assurance that you have not just found one trial in which you could not distinguish anything from anything.

(Slide.)

There are many situations in which active control equivalence trials are quite credible. Bacterial infections, deep vein thrombosis, highly responsive tumors, these are all situations in which the difference between no treatment and treatment is obvious and perfectly clear so active control trials are used in those settings.

(Slide.)

Obviously you cannot deny patients therapy that prevents irreversible harm. You can in our view ask people to delay or omit treatment of symptoms. Active control equivalence trials are unfortunately not credible in many situations because without placebo you cannot tell whether there is assay sensitivity, that is the ability to distinguish anything from anything. Placebo control trials can sometimes be made more attractive to patients and physicians and made ethical in some cases by modifications of study design. The fifth one is not treat them.

Thank you. I hope I did not go over too long.

DR. CHILDRESS: Thank you very much. This is obviously exceedingly important for our discussion of research involving

decision impaired subjects and for our further discussion of international research.

We will take -- try to do about eight or ten minutes and then move into the public hearing. So it is open for questions.

Alex?

MR. CAPRON: I want to make sure that I have understood the point. If we were willing to say that the only measure of success would be showing a significant improvement with the new drug then the fact that an existing drug might be performing only a placebo effect would not be a problem, is that correct?

DR. TEMPLE: If you show superiority to the standard therapy that is always interpretable and if that were to become the standard for approval then, yes, this would not be a problem.

MR. CAPRON: So the impediment there is the disinclination of the developers of drugs to develop drugs against a standard that what they come up with is better than what we now have?

DR. TEMPLE: Yes, although that is a long discussion. For example, many people would say that the new category of antidepressants, the serotonin uptake release inhibitors, are of great value because they have a different array of side effects. But in a large number of studies no one has been able to show that they are better than tricyclics because they are not.

MR. CAPRON: So what you are saying is that the measurement of improvement might have to be refined? That is to say if you could show a difference in side effects or adverse consequences and make that one of the criteria that you are using that improvement on that score and equivalence would be demonstrating a difference but that would not do it?

DR. TEMPLE: Because you would not know whether the drug worked at all. And showing fewer side effects, water can show fewer side effects, but you really do have to know that it is having the favorable effect on impression. It is not a boon to people to give them a low side effect ineffective antidepressant.

MR. CAPRON: Then does it depend upon -- the point being made in favor of using active controls is that you do not want to -- and your agreement you would have to use it in situations in which you have a serious condition which if treated with a placebo could lead to disaster. Another way of stating that vis-a-vis the side effect question would be are you facing with existing treatments side effects that are so severe that an improvement on that score would be significant and then you would -- you might need a pairing of trials.

One trial perhaps more limited to show that you can have an effect over placebo on the major indication that you are using this for, depression or whatever it is, and then other active controls to show whether or not this drug is superior in removing or limiting or decreasing the side effect that is serious enough that you want to develop something better than the existing treatment to

get rid of that side effect.

DR. TEMPLE: Well, yes, in part, but you also have to know how -- if you want to say that something has fewer side effects you also want to know in that very trial something about the relative effectiveness of the trial. You do not want, for example, to use a very low dose of one drug compared to --

MR. CAPRON: Right.

DR. TEMPLE: So you really do need to know to make an intelligent statement there, you really do need to know whether you are having an effective therapy. Now there are some side effects that you could test in an active control trial. As usual, though, if you did not see a difference you would be -- then you really would not know that they are equivalent unless you had some kind of control to show that --

MR. CAPRON: Right. But if you do develop a drug and you have no difference over present treatments why should we be interested in seeing it approved? I mean, if that is --

DR. TEMPLE: Well, that is a fair question. If it is unethical do a trial. You just cannot do it -- you know, you just cannot do the trial. If it is ethical to do the trial then you have to ask do you want a variety of therapies for the same condition? Many people would say that in depression people respond differently to a wide array of drugs. All of these drugs have subtle differences. Every one of them. They are not -- we classify them as SSRI's but they are not all the same. They have different interaction capabilities. They have very different durations of action. They are all different.

The idea that because a drug is not -- I mean, it is hard -- you hardly ever get a drug that is better than another drug. I mean, the examples of true superiority are so infrequent that, you know, yes, TPA beats streptokinase; yes, clozapine beats some other drugs. Those things happen. Yes, Omeprazole beats H2 blockers.

But in the enormous majority of situations the drugs really cannot be distinguished on effectives.

That does not mean if you did thousand of patients you could not find some difference. Maybe that is true. But I think you have to ask whether that would be worth it. A difference that tiny is probably not clinically important.

So it is a fair question to ask do we need this but that is a different question. I am just asking if -- assuming you do how can you provide evidence?

DR. CHILDRESS: I have three people. Alta, Diane and then Bernie.

MS. CHARO: Dr. Temple, also by way of clarification if I may, there were a pair of slides that you showed us in which you showed six trials that compared -- was it Imipramine and a --

DR. TEMPLE: Imipramine, Nomathensine and placebo.

MS. CHARO: Thank you. On the first trial they showed

the same effect and then you showed the placebo arms and then stated that, in fact, they were not better than placebo. Now I thought you showed the slides to draw the lesson that without the placebo arms you cannot really know what you are looking at but I found myself thinking that the lesson was that the standard therapy was not better than placebo.

I wish you could help me understand better why that is not the lesson to be drawn here.

DR. TEMPLE: Well, the point here is that drugs that for a variety of reasons we believe work -- I mean there are hundreds of studies showing that Imipramine is an effective antidepressant but in these six trials for reasons that I cannot tell you, it could be partly sample size but it could be the population just got better spontaneously. That is my favorite choice here. These trials were not able to tell a drug we know to be effective from placebo. And unfortunately that happens all the time.

I can show you the duodenal ulcer trial -- the ulcer trial that cymetadine, a drug that we know heals ulcers, in two out of the first four trials we ever saw could not distinguish itself from placebo because ulcers heal by themselves a lot and because there is some uncertainty about whether an ulcer is healed or not.

You are looking into, you know, a dark place and you do not necessarily look in the right place. Who knows? There is some variability but the message is -- you sort of have to believe this -- that those are effective drugs. We did not know about Novafemsine (?) because that was the drug we were studying but we are pretty sure imipramine is effective. There is hundreds of trials to show that it is.

But in five out of those six trials that used the three arm design the studies could not tell anything from anything. It really is just what Lou Lasagna said, you see that in analgesic studies all the time. Some populations just are not good assays.

MR. CHARO: So again by way of Alex just wanting to understand the thrust of your talk the value of the placebo trial -- the placebo arms really is as a check on the quality of study design? The bottom line.

DR. TEMPLE: You are absolutely right.

MS. CHARO: Okay.

DR. TEMPLE: It is the internal standard. It proves that this was a study that had what I have been calling assay sensitivity. That is you have a bulb in your colorimeter. You can tell that -- this is a trial that can tell completely inaccurate substances from a true antidepressant. I mean it may seem surprising to think that all trials do not but the experience is that they do not.

MS. CHARO: Okay. If that is the case, and this is really the question, I am sorry it took so long to set it up, but if that is the case then is there a way to structure a trial so that you have as an initial step a placebo arm that is designed really as

a check on the quality of the study design and once you have done a quick check with a relatively small number of people on the quality of the study design you then move on to the substantive study itself which drops the placebo arm because you no longer need it. You check your design and it moves on to an active control study.

DR. TEMPLE: Well, you will see in the materials that I handed out on study designs that is one suggestion that is perfectly good for some situations. For example, I think it would be reasonable -- if you wanted to do a study of long-term antihypertension treatment you are not going to leave people untreated for six months. But you could show that the population is sensitive to the drugs by doing say a four week placebo control trial by designing a three arm trial with two active drugs and placebo and dropping the placebo group after a certain period of time. Yes, I think that would be quite informative.

If you wanted to do the same thing in depression, depression is a little tricky, it is not clear whether you are looking at long-term effectiveness or preventing relapse, but a very typical way to do these trials now, and we have encouraged this, is you do your placebo control trial, you take the responders on drug preferably and then you follow them out for four months, six months, however long you think is necessary, and then you take the drug away for a relatively -- well, you take the drug away from half the group. Do a randomized placebo withdrawal and as soon as people relapse to a degree that is measurable you drop them out of the study and you have an answer and nobody has been on a drug that did not work for very long.

But you sort of have to have a will to produce a different showing trial to dream up these designs and I think that is our point. You do need that to be informative but you can make the trials minimize exposure and things like that.

MS. CHARO: Thank you.

DR. CHILDRESS: We will take the last two questions and then move into public hearing.

Diane, and then Bernie?

DR. SCOTT-JONES: I have a question about placebo control trials, about the problems with those trials other than ethical problems. For example, showing a difference between two groups depends to a large extent on sample size itself and some of your charts showed sample sizes which varied greatly from study to study. So could you comment for us on problems that exist with placebo control trials independently of ethical problems?

DR. TEMPLE: In a placebo control trial if your sample size is too small you do not win. So people have a strong incentive to make the sample size adequate. In fact, in depression the reason people do three arm trials now is that they have found commonly that they could not distinguish the drug from placebo. Well, if you cannot distinguish the drug from placebo does that mean your drug is no good or the study is no good? You cannot tell.

So if you include a third arm, an active control -- see, we would not insist that there be a third arm all the time but most antidepressant trials now include an active drug, a placebo, and the new drug. Then if neither drug beats placebo you toss it. It is no embarrassment because this was a poor study that could not detect -- tell anything from anything.

If the active drug beats placebo and your drug does not you might want to consider dropping development of the drug because you have learned something. This was a drug that had assay sensitivity and you lost. Sometimes that happens anyway so you might want to have that twice.

But in any trial when you fail to show a difference, whether it is a placebo control trial or an active control trial, you do not know whether it could have shown a difference. So three arm trials are very informative and we and the Europeans actually are urging that kind of trial in many cases.

DR. CHILDRESS: Bernie?

DR. LO: I want to thank you for tackling this hard topic. I wanted to sort of underline the importance of looking at the totality of the evidence on the effects of a drug and not just on one trial. You sort of suggested that there are some situations like solid tumors -- I am sorry -- post-MI treatment and leukemia where it is so well known the treatments are effective that you could not possibly, you know, run a placebo controlled trial.

But how you interpret when something -- when a drug crosses into that category of we are sure it works and when it is in the class of there is legitimate debate and a lot of people think it works but some people are not quite sure, it seems to me there is a very tricky issue and, you know, who gets to design using what criteria are tough issues.

With regard to your comments on equivalency studies that do not include placebo it seems to me it makes a big difference when you think you are sure the standard therapy really is effective or not because if you ran an equivalency study without a placebo arm and you could not show a difference such the trial was adequately powered to detect the clinically meaningful difference, it seems to me what you would have to do is say, "Let's look at all the other evidence. Are there other similar studies with different populations that also did not detect a difference?" You sort of have to put together all the data you have from similar studies of the drug versus the standard therapy.

And in a sense rather than trying to look at one pivotal equivalent study I think you really need to do a series of studies and sort of interpret the totality then and it is not just one study. I mean, I know the practical problems of whether a drug company is willing to invest that much in a drug up front but it seems to me some of the problems that come up by not being able to tell it is just a bad study and you got unlucky with that patient population or something versus the drug does not really work can

only be answered by looking at external evidence to the trial and not just looking at your own trial.

DR. TEMPLE: Well, in some ways that is the trouble. You have to bring to bear external evidence. The trial itself in an equivalence trial does not tell you whether the study had assay sensitivity.

So, for example, considering an antidepressant if I know with a large experience that something like a quarter to a third of all the trials that people carry out trying to show a difference, that is they are doing their best, with sample sizes that have grown from the 30 in the example I gave to 80, 120 and 200, and I know that I still cannot say with some assurance that an active drug can be distinguished from placebo. I just cannot find in a finding of equivalence credible evidence of effectiveness.

DR. LO: In one study --

DR. TEMPLE: Well, as I said the last thing on my slide was redundancy. But it would have to be considerably redundant and nobody has worked out at what point something like that becomes persuasive. But, for example, in considering thrombolytics we knew that every thrombolysis trial has shown about a 20 percent reduction in mortality. So with an advisory committee we worked out what would constitute an equivalency finding or a not inferiority finding which is really more what it is that would be persuasive as to the evidence -- would be a persuasive showing of a new thrombolytic.

There are probably a number of situations in which you can do that. I doubt you can ever do it for depression or OCD or some of those things because they are so variable. But you could probably do it for antiemetic therapy because the effect is quite dramatic and pretty much the drug always wins if you pick the right patient population. So someone can do it and you are perfectly right, the more times you fail to distinguish the more credible it might be.

But I am worried about that second problem which is the incentives to really doing a good study are not automatically there. We could try to say, oh, well, it has got to have these characteristics and so on but there is nothing like self-enforcement.

DR. LO: I guess then as a broad comment it seems to me to be very important then to set up explicit criteria for what are the clinical situations based on what considerations that you would find an equivalency trial acceptable versus a placebo trial?

DR. TEMPLE: Well, we sort of have in a way. What we basically told people is if you think this is an appropriate design here is how to make your case. You know, the people who want to do something are the best able to support it. They have to survey the literature. They have to look at the experience and make the case that this is an interpretable study. We are certainly ready to listen. What I am mostly trying to describe is what the problem is and what the burden is. Whether in a particular case it is credible

I think you have to make judgments and different people reach different judgments. Different countries reach different judgments on these questions.

DR. CHILDRESS: A quick last question, Harold, and then the public hearing.

DR. SHAPIRO: Thank you. One just brief comment. It seems to me from your written material and what you said today that if the incentives are wrong we could at least consider the possibility the wrong people are doing these trials. Put that off to the side for the moment.

Do I interpret the fact that so many trials -- in so many trials a drug known to be effective fails? Is it right to say there are probably a lot of lousy trials out there? Is that what I am --

DR. TEMPLE: Well, see if we do not -- I do not know the reason that they fail. I do not know -- because, you know, there was no placebo there. I do not know -- I am sorry. I do not know the reason. People speculate on this. For example, some groups with depression that you put into a trial all get better right away. Now it is not obvious from looking at the entry criteria why that happened. Maybe the people doing the trial are just too good at psychotherapy because there is some evidence that psychotherapy works. Maybe they obliterated the chance to show a difference.

But I think it is like Lasagna said. You just do not really know why it happens that way. These are diseases with a lot of influences on them with variable manifestations where the measurements are not very precise and I do not think there is evidence that it is anybody's fault.

Let me go back to the other thing you described. People have -- realizing that active drugs do not show up, people have gone to great imaginative lengths to undertake procedures that would exclude people who would diminish the ability of the assay to show anything.

For example, everybody knows exercise tests are very hard to run. They are very variable. Many patients cannot get the same result in consecutive days. So there are now screens if you are doing a heart failure study or an angina study, there are now screens of people during a period to see if they can give a consistent exercise test. You know, you are sort of checking your assay.

You would not know a priori that you have to do that and I do not think it would be evil of people not to have realized that it was necessary. Now we know it and people develop ways of making the assays at least somewhat more sensitive and so intelligent people trying to show that their drug works use them.

I am not trying to make -- I would not make the moral judgment. We are very practical. What I like to see is people to have a really strong incentive to do the best possible trial. That works best. If we were smart enough we could perhaps tell people

how to do that all the time but I do not think you can know all these things ahead of time by just thinking about them. You sort of have to get the experience.

DR. CHILDRESS: The chair is a softee and has called for no more questions but one more. One brief question. That is it. We are going to behind and have an allocation problem.

DR. BACKLAR: Thank you very much, Dr. Temple. You mentioned a few situations in which a placebo trial would not be in order and then in passing you said something about people with epilepsy. Did you consider that particular group of people not to be in order for a placebo trial?

DR. TEMPLE: Well, yes and no. Most people believe that you should not take patients with epilepsy off their therapy, whatever it is. But there are many patients with epilepsy whose therapy is not satisfactory and who continue to seize. So the standard way of developing an antiepileptic now is to leave people on whatever therapy they were on and then add either the new drug or a placebo. Okay. So you get a trial that shows a difference. They have fewer events.

What you learn is that the drug works in combination. Now that is not everything you wanted to know. You wanted to know whether it works as monotherapy. There are designs in which you gradually take away the other therapy and see what happens that have been tried. Or sometimes you just do not have the answer on monotherapy. But you definitely have evidence that the drug has an effect on seizures and you have not kept anybody off therapy.

In angina there was a lot of controversy a while ago. People thought that to do an angina trial you had to take people off all therapy. Well, that is not true. You leave them on their nitrates. You could even leave them on their beta blockers and study a new drug in comparison to a placebo as in addition. That is informative. That is how all heart failure drugs are worked up now because you cannot leave people off their ACE inhibitor. You have to give them that. It saves their lives.

On the other hand it is useful and valuable to the public to know that if you add this other drug to that situation you do even better. It is a very informative kind of finding. So we recently approved a drug called carvatalol (?) in that way. So we do not know whether carvatalol works by itself but, you know, that is not that important. Add it to the beta blocker -- add it to the ACE inhibitor and you will do even better.

DR. BACKLAR: So you could use this kind of design, study design, perhaps with people with schizophrenia?

DR. TEMPLE: You could if it makes sense. The examples that I gave all involve drugs that are pharmacologically distinct. But, for example, in depression to study a new tricyclic by adding it to a persons other tricyclic that would not make a lot of sense. If the drugs are using the same mechanism in schizophrenics I do not think that will make a great deal of sense. If it was a different

mechanism then it certainly would.

MR. CAPRON: Could I just ask for a clarification? Excuse me, but when you approve the drug is it approved only for use with?

DR. TEMPLE: Yes.

MR. CAPRON: And that does not prevent physicians from using it without the other drug?

DR. TEMPLE: No. But, you know, they know that -- there are not any data on that and that they are on their own. But I am sure that they do.

DR. CHILDRESS: This has been a very informative and helpful presentation. We are grateful to you, Dr. Temple, and also for providing the written materials. Furthermore, there may be after this discussion some other materials you would like to provide us and we would be grateful to receive them.

In addition, if you are around as long as the break I think there are still some other questions that individuals might want to raise.

DR. TEMPLE: Sure, I will be glad to. The second paper I handed out was a general discussion of study designs that might avoid some of these problems.

PUBLIC TESTIMONY ON THE ISSUE OF THE COGNITIVELY IMPAIRED AS RESEARCH SUBJECTS

DR. CHILDRESS: Thank you again. All right.

We turn now to our public hearing which is an indispensable part of our effort to chart our course, our direction or a report on decision impaired research subjects and possible guidelines or special protections for those subjects.

Several people have already indicated, and their names appear on the sheet, that they would like to present in this period. If there are others who wanted to present on this particular topic, that is decision impaired research subjects, do -- I guess Pat Norris is at the desk? Pat Norris is here. -- do indicate to her that you would like to so we can try to be aware of the time as we are moving along to be sure we get everyone in.

We will have subsequent public testimony on other topics relating to research involving human subjects. Today we are looking only at decisionally impaired research subjects.

We are grateful to those who have responded and their names appear on the list. We will go down the list in alphabetical order but we are treating the discussion of the New York case, T.D., as a separate matter and will hear from the different parties involved in that later this morning.

We are also grateful for the written testimony that several of you have provided. Several of you are planning to testify orally today, as well as others who could not testify and who also submitted written testimony.

We will ask each person, and we have indicated this in advance, to restrict his or her initial comments to five minutes and

given the fact that we have already lost a lot of time and out of fairness and equity to others who will be wanting to speak I will try to be a stronger chair and enforce that.

We will want to have an opportunity to ask questions so it is really important to stick to the five minute limit so we will have a chance to engage you in discussion because there will be things that we would like to raise with you to again help us think through this project.

All right. If we are going now alphabetically is Mr. Robert Aller here?

All right. Thank you for joining us.

MR. ALLER: My name is Robert Aller. Can you hear me okay? And my son, Gregory, actually was a participant in a schizophrenia research project at UCLA. And at the time I had actually personally seen the benefits of human subjects research prior to my son entering the project. Between the years of 1964 and 1988 I had been employed to document on film a UCLA Department of Psychology research project to develop new teaching techniques for autistic children. I found because I was working with the researchers all the time that they demonstrated extraordinary care and concern for the children and their families and the families were always fully informed of what was happening.

When our son was diagnosed and joined the UCLA research, the Schizophrenia Research Program, I had anticipated experiencing the same kind of researcher concern for the welfare of human subjects that my wife and I had seen in the autism project for a period of almost 25 years. However, what we found was something very different.

By 1989 at UCLA Greg was taking antipsychotic medication and he was actually earning a 3.8 in college and working 15 hours a week so he was really doing quite well. And at that time we thought that the experimental aspects of the research were benign from the informed consents and fliers that they gave us.

The researchers told us at that time that Greg might not even have to take antipsychotic medication and it was recommended that he participate in the crossover and withdrawal protocol. While the consent form stated with equal emphasis that he may get better, stay the same or get worse, the researchers did not reveal to us that in a previous year over 92 percent of the subjects got worse.

After the medication withdrawal Greg suffered a lost of intellectual functioning. He became violent and our family was devastated in the process. After remedication he failed to return to his previous level of functioning and after waiting six months my wife and I decided to go see the UCLA Vice Chancellor of Research and discuss the issues that we had been confronted with.

In that tense meeting with the Vice Chancellor and the Chair of the Human Subjects Protection Committee and the Administration we told them that we thought that a murder or suicide could occur in this research based on our experience, and we also

asked for Greg's records at the time so that they could be evaluated.

In response, only a few of Greg's records were made available and about two weeks later at 8:30 in the morning as students were on their way to their classes another human subject in this research, Tony LaMadrid, jumped off the engineering building committing suicide.

At that point we, of course, were quite, quite concerned and the LaMadrid family and two more families were joined with us in filing complaints with OPRR and I think we may have been the first group of families to speak out about abuse in the schizophrenia research.

OPRR conducted an investigation and determined that the consents were deficient and that Tony LaMadrid had been in a monitoring phase of the research that did not even have a protocol.

We found NIMH was vigorously defending the research conducted without proper informed consents and it reminded us of the U.S. Public Health Service's defense of Tuskegee.

But a public debate ensued in professional journals and the researchers seemed to be claiming -- and these are journals that are even published just up to now -- claiming that schizophrenic patients are able to comprehend consent. There was no proof that anyone had been hurt and that everything in psychiatric research is really all right.

We are here today to say that everything is not all right from what we have observed. Administrators at NIMH have been authorizing protocols that inflict unnecessary harm on vulnerable people. We believe that there is a serious imbalance that favors the researcher and leaves the human subjects inadequately protected in the process and that imbalance should really be corrected.

Consent forms are often ambiguous and misleading either by omission or vague language. To strengthen the system of protection of human subjects we have several suggestions in this time limited period here.

Medical doctors not connected to the research should represent the best medical interests of the human subjects. Nonhuman primates already have that protection. We think humans should also have that protection.

Informed consent documents should no longer be blanket forms but instead should reflect the medical history of the individual human subject.

Alternative treatments should accurately reflect the alternative treatments that are actually available for that individual human subject.

Risks should be put in rank order of probability. Something that people have avoided doing.

Consents should be truthful and forthcoming and even blunt.

The risks are too great to camouflage the foreseeable

outcomes.

The vulnerable populations that we are concerned about cannot be compared to football players out on the field who when injured can have a knee operation.

Researchers have reported that following psychotic relapse some patients never return to their former level of functioning. No operation is possible to correct that kind of harm.

I, for one, do not believe that researchers should conduct protocols that cause harm by design. Vulnerable patient populations already have a high rate of suicide. How many are we going to knowingly harm?

"There was nothing in the experiment that was unethical or unscientific." Of course that is Dr. John Heller speaking, a former director of Tuskegee.

We found that that same defense was offered for research that has harmed those who are decisionally impaired. Some of the cases presented today will hopefully represent properly conducted research and researchers should be applauded when that happens. We know that happens all over the country. However, some of the cases presented today will raise some troubling ethical and scientific questions.

Thank you.

DR. CHILDRESS: Thank you. And thank you for sticking pretty close to the time limit.

Questions for Mr. Aller?

DR. BRITO: I have a question, Mr. Aller. Thank you for your presentation.

Just out of curiosity do you know what the findings of the study your son was involved in? What the end result -- what was found or were you informed of that?

DR. ALLER: Yes. I would not want to summarize it. I think they did find that everybody needed medication or that is what they said.

DR. BRITO: My understanding is that what bothered you most is that you were not informed of the previous year's findings. How much time was taken with the informed consent?

DR. ALLER: Well, actually they omitted a couple of crucial things and what we find in informed consents that is omitted that I think is most egregious is the alternative treatments because very often the alternative treatments would be a better choice. So they omitted alternative treatments and risks when they knew what the probabilities were.

DR. BACKLAR: Thank you, Mr. Aller, for coming to testify before us.

Could you tell us a little bit about when your son agreed to be in this trial as I believe there was some connection to clinical treatment as well as being in a research protocol? Were you or your son confused by this?

DR. ALLER: Well, it was called the After Care Clinic and so what was not clear in the presentation -- what was clear from the brochure is that you are going to get the best treatment available. That is what the claim was. And there was no up front claim that you are probably going to have a relapse. There is some dispute. The researchers claim they did everything orally and, therefore, it is okay. But we feel that the federal regulation should be complied with and these things should be spelled out in a written form.

DR. BACKLAR: But I want to ask this question again. Did you believe that your son was going to be in treatment, getting clinical treatment?

DR. ALLER: Well, we were aware that they were making observations and collecting data. We thought he was getting the best clinical treatment, absolutely.

DR. CHILDRESS: The last question from Eric.

DR. CASSELL: Do you think that you would have benefitted from a summary of the findings of the study thus far, that is your son entered at your point and another person entered at this point, that you should have known the findings thus far?

DR. ALLER: Very definitely. That should have been in the consent forms that the data that they had collected should have said that on average 88 percent or 75 percent or whatever percentage had adverse reactions to this experience. Yes.

DR. CASSELL: And then a subject entering in the beginning of the study would be somewhat different than a subject entering halfway through, and then so forth?

DR. ALLER: Well, not really. They already had data from other studies that they could have shared with us. I think the idea of full disclosure is a real problem for researchers when you are in high risk research. They could have disclosed that in other research there were no relapses while on medication and there was a high rate of relapse off medication.

DR. CHILDRESS: Thank you again for sharing this with us.

Our second speaker is Ms. Janice Becker, who has also shared with us a document that I think has been put in everybody's place book.

Thank you for joining us, Ms. Becker.

MS. BECKER: I want to make it clear that no organization represents me and no one has told me what to say. I have expounded on my experiences in my written testimony which I have submitted to the commission.

My daughter, Laura, was hospitalized at age 18 with schizophrenia. Antipsychotic medicines failed to alleviate her symptoms. Eight years later she was, indeed, institutionalized.

The Maryland Psychiatric Research Center seemed a chance to alter the dismal course of her life. In our interviews with the department director and social worker they emphasized the quality of

patient care at MPRC.

A few months after her admission drug washouts were done and it was heartbreaking to watch Laura's condition deteriorate. She became very psychotic and exhibited severe involuntary muscle movement. We had not expected that she would be required to endure such painful symptoms without medication for years. Nor had we expected that she would be given drugs that would make her psychotic symptoms worse. It was a terrible time.

In fact, during Laura's entire stay at MPRC I know of no medications given to her that were aimed at alleviating her pain and symptoms until she was to be released.

We repeatedly asked for research protocols but were given evasive answers. Finally we received them and found she was already in a study and likely without informed consent. We found that most of the studies were protocols for haldol. We found that her allergy to haldol eliminated her as a candidate.

Our condition for Laura's admission was that she not be given haldol because of a severe dystonic reaction that she had previously suffered. In fact, she was used in some of the haldol studies. There were at least three times she was put on haldol and how many others we do not know.

Twice I visited her and found she was tied to a chair. The pillow cases which tied her wrists and ankles and the sheet tying her waist were soaked in perspiration. The knots were so tight that it took the nurse and me twenty minutes to untie her. She had also been given wet sheet wraps and cold baths. These restraints were prohibited in state hospitals. Did this not apply to MPRC?

I witnessed six staff holding Laura down until she was quieted. In another such incident her face was cut requiring sutures.

The program director called requesting a meeting as soon as possible with her and the chief of the inpatient program. At this meeting my husband and I were confronted with the fact that our daughter was three months pregnant. We were horrified. For two years Laura had been in a locked research unit and in a severely psychotic state. This was a criminal offense. To my knowledge there was no investigation to determine whether she was raped by a staff person, a patient, how often or if it was continuing.

I felt pressured to make an immediate decision for an abortion. We were then told to pay for it. When I asked if other research subjects had become pregnant while they were there I was told only three times. Why did it take three months for them to discover her pregnancy? I wanted her out of there but I was afraid of what might happen to her. I felt trapped. Laura was off all of her medications. She was in the worse condition I had ever seen her in and at times she was even dangerous.

How could someone actively psychotic and disoriented leave? A state hospital would seem an obvious place for Laura but I

was concerned their deteriorating conditions. Bringing her home in that condition was certainly not a solution.

Laura, so ill, so vulnerable to pressure, and lacking an insight could not be expected to make informed choices.

Other families whose loved ones suffered similar inhumane treatment talked to me about their experiences at MPRC. We shared many of the same concerns and frustrations. We also questioned the scientific justification of keeping a patient on a locked ward for nine years without medication. This and many things left us with a feeling of helplessness. None of us knew where to turn for help and I do not know where to turn for help now.

What did the Laura's suffering and the suffering of others accomplish? Did anyone ever consider what effect this would have on the quality of their life or is that no one's concern?

I want a full investigation of the past, present and future practices at MPRC. I want consequences for wrongful actions. The inpatients need an autonomous doctor to ensure that the mentally ill are not exploited for other people's purposes.

Why are research animals better protected legally than human research subjects?

It is my sincere hope that this commission will promote these changes. No one should have to endure physical abuse, humiliation, or pain in the name of research.

Thank you.

DR. CHILDRESS: Ms. Becker, thank you very much for sharing that with us.

MS. BECKER: You're welcome.

DR. CHILDRESS: And also for the extensive written testimony.

Are there questions for Ms. Becker?

Alex?

MR. CAPRON: Some of the things that you have documented here go back a decade. What has happened since then? You have obviously raised these complaints. Have you had any response?

MS. BECKER: Raised them to who?

MR. CAPRON: Well, I cannot tell but I assume you have raised them to officials in Maryland to start off with.

MS. BECKER: Yes. I have raised some complaints. Well, actually I have given testimony at some other seminars and things trying to get the message out. I have not written my legislators, no, if that is what you meant.

MR. CAPRON: Or the attorney general?

MS. BECKER: No. You know, to tell you the truth the four-and-a-half years that my daughter went through has taken me much longer to get over because I feel guilty. I feel guilty because I was the one who wanted her in the program to break the hospitalization and maybe get her out in the community, and I have had some problems getting over that. And what documentation I had -- I do not have the protocols. I have written for them and -- I

mean her medical records -- and they have not sent them.

But she is in the community and doing some better and she does consume a lot of my time and quite frankly I just wonder what good would it do as an individual. You know, I felt very much alone. I knew there were other families that went through it but it gets a little nerve wracking going over this and over this with different people when it is not effective.

So I had hoped, you know, that I had come to the right place finally.

MR. CAPRON: I do not think so. That is partly why I raised that.

MS. BECKER: Okay.

MR. CAPRON: I think this is a general issue for us. I think it is important that we hear these stories to have a sense of what is going on. But we are not an investigatory commission. We do not have the power to conduct investigations nor do we have -- particularly as to facilities which are not federal facilities any direct oversight at all. It would be a mistake if people came to us with the expectation that they had now put their case before a body which is in the position to do anything about it.

That is why I asked my question. It was not to be critical of you at all, ma'am. I can well understand the difficulties that you face and I applaud your willingness to come and share this story which is painful to tell with us.

But it is important that we have some understanding of what our role is and it is also important that you realize that we will not be in a position to subpoena those records, to hold an investigation, and to hold people accountable the way that maybe some state officials could do that. I do not know the situation there in Maryland but we are not in that position and it would be a shame if people coming before us today thought that was what was going to come out of this hearing.

DR. CHILDRESS: Thank you very much, Alex, for making that point.

At the end of your remarks when you were talking about things that you hoped from NBAC one was the line that Alex pursued and obviously we cannot do that. On the other hand you made some recommendations about autonomous doctors and that gets close to the kind of issue we can consider. What sorts of -- and that was raised also by Mr. Aller -- we can -- we are going to consider possible guidelines and how they might be used in research with decisionally impaired subjects. That really is our task.

Thank you very much for sharing your story.

We will have to move along steadily because we have four additional people who have indicated -- who have arrived today and indicated they would like to testify.

Our next speaker is Mr. Joseph Friend and his statement has also been circulated.

I thank you, Mr. Friend, for joining us.

MR. FRIEND: See I want to start with a statement that I am speaking for myself and I want to start to say that I very heartily support research because with research on human subjects my son has medication available to him today that has made him in better shape than he has been for many years.

I am a retired naval officer and later I worked for the State of Maryland. In between I worked in social programs in the innercity, an HMO Medicaid program, and have had extensive experience in the participation of the communities in the processes that they are involved in.

I know that there are many good people in research but I know that research is a bureaucratic institution and bureaucratic institutions have a way of manipulating situations that are not the intentions of those people that work in them.

Now I want to tell you my son's story because I think it does fit in with what you are trying to do. My son is currently 34 years old. He has had psychiatric problems since he was six years old but he has had excellent care in Army, Navy and Air Force medical facilities. So we grew with a trust for the medical establishment.

When he was a junior in high school he had a full blown manic depression episode. He refused treatment but finally agreed to it and so in the summer between his junior and senior year he was stabilized and put on lithium.

Things went along fine. He went into college in the Maryland Institute of Art and he started deteriorating. He then went to Europe to join a program with the agreement of his psychiatrist called "Youth with a Mission." There he went off his medication, was found wandering in the airport in Amsterdam, and I had to go and pick him -- when I got there he was actually in a catatonic state and I got him to Wiesbaden and he was air evac-ed to this country.

He was in the hospital for four months. When he was released we got him into a local program in our community and then my wife and I looked at his background and we talked with him and thought that his situation might be helpful in research in order to help him and other people like him. So we approached the Walnut Street Clinic, which is the outpatient clinic of the University of Maryland Psychiatric Research Center at Crownsville State Hospital.

Part of the protocol is they said, "Well, he had to have a baseline condition," which frankly means a washout. They said, "We will monitor him," and he stayed at home. In the third week -- he was supposed to be off for four weeks. In the third week he went -- the day after he had one of his visits he went completely psychotic. We called the institute and we were supposed to bring him in the next day but during that night we were watching him and trying to watch him. Finally my wife came to me when I was taking a rest and said, "He is laying in the street in front of our house."

I got him back in and I just happened to notice there

was a bottle of about 200 aspirins that was almost empty. I called the Poison Control Center. They said, "Get him to the hospital." We were four minutes from the hospital. I do not know if you know what death by aspirin overdose is but it is internal bleeding and it is supposed to be very painful.

Needless to say we withdrew him from the program. But my point is, is that I would hope this commission would recommend and mandate that washouts, because I understand there are other ways of doing it, be eliminated from any research protocol. It is dangerous to our relatives.

Now the next thing is I talk about my experience in government. There are things called Institutional Review Boards, IRB's. I want to say that these boards are the stealth weapon of the research bureaucracy. No one knows who is on them and even the New York Times wrote an editorial saying, "Many times they are rubber stamped." I would hope that this commission would recommend that at least 40 percent of each IRB would be composed of consumers and families.

The family movement has gotten millions of dollars into research but it is as though the researchers say, "Hey, we want the money but just trust us." If this happened it would mean that research protocols would have to be written with a sensitivity towards families and they would have to be written in nontechnical language so everybody understand what was really going to be done and all the implications would have to be spelled out.

Now there would still probably be mistakes but the thing is that is a type of participation that would bring accountability into the research system.

Thank you.

DR. _____: Thank you, Mr. Friend, and thank you for connecting some recommendations to this important story.

Alta, do you have a comment?

MS. CHARO: Yes. In some ways actually I actually would like to say something to you as well, Mr. Friend. But as a follow-up to Ms. Becker I felt one thing that got omitted is that although this commission does not investigate specific instances we try to draw lessons from them. It is important to say for the record what specific instances can generate.

I think that they need to generate a complaint to the Office for Protection from Research Risks and I think for all of these kinds of stories that we are hearing people should know there is a place to go. The Director of the Office for Protection of Research Risks is in the room today. There is a phone number that they can start with to start the ball rolling and find out how to file a complaint, which would be 301-496 -- that is the old number. What is the new number? 301-496-7005.

And the second thing is that when there is evidence of criminal activity it is important, as Alex had kind of implied, to take advantage of local authorities, both the local DA and the

attorney general as a follow up when it is possible for you to do that.

But I would not want to leave people with the impression here that because we do not investigations we also are not concerned about the specific incidents we are hearing about.

Mr. Friend, specifically from the testimony that you gave and your suggestion about the composition of IRB's, do you believe that the kinds of suggestions you are making are those that are particular to people who are being enrolled in trials that have to do with psychiatric medication or are these kinds of suggestions ones you would say are generally applicable to people that are going through cancer trials or trials of, you know, headache remedies and antihistamines? I am trying to get a sense of whether you are looking for special procedures for people with psychiatric illness or a more general recommendation.

MR. FRIEND: Well, my specific recommendation, of course, was related to human subjects of psychiatric research. But in the broader sense I think any Institutional Review Board should have community participation because it does put a better sense of accountability into it.

MS. CHARO: Thank you.

DR. CHILDRESS: Other questions?

Thank you very much, Mr. Friend.

Our next speaker is Ms. Arlis Neason.

Is Ms. Neason here?

MS. NEASON: Yes, I am.

DR. CHILDRESS: Okay.

MS. NEASON: Good morning. My name is Arlis Neason and I am here to introduce my son, Jeffrey Neason, who is going to --

MR. NEASON: I am going to turn 15 this September 29th.

MS. NEASON: Jeffrey was born premature weighing 2 lbs, 15 ozs. He remained in a pediatric intensive care unit for nearly seven months before he was discharged home weighing 5 lbs, 4 ozs. Twenty-five diagnoses are listed on his discharge summary but failure to thrive and a chronic diarrhea prevailed throughout his childhood even to the present day. Exploratory bowel surgery was performed when he was only four months old. There was a time when he was not expected to live.

As a result of his debilitating symptoms his education and his social interactions were compromised. For years his physicians diagnosed malabsorption syndrome. At age 8 his medical records discussed the possibility of Crohn's Disease. Because of his chronic diarrhea with associated weakness and failure to thrive my husband and I brought Jeffrey to UCLA Medical Center seeking medical treatment.

His first appointed was during January 1992 at which time he was evaluated for three days. We all returned to UCLA during February so that Jeffrey could be further evaluated. After several more days of testing an accusation of suspected child abuse

was made by Jeffrey's pediatric gastroenterologist. We were accused of poisoning Jeffrey with laxatives. Precisely at the same time the false allegation of child abuse was made Crohn's Disease was also diagnosed by this same accusing doctor.

Jeffrey was taken immediately from us and admitted to the pediatric intensive care unit on February 26th. He was labeled a victim of Munchausen Syndrome by Proxy. Today we know that Jeffrey was held without legal authority when he was taken from us.

The first hearing was in California on April 6th, 1992, related to custody. Our Nevada residence was searched looking for laxatives but none were found. More than three years passed before our family was reunited on May 1st, 1995. A University of Chicago pediatric gastroenterologist and four Mayo Clinic physicians all refuted UCLA's child abuse allegations. We were triumphant at trial.

Jeffrey remained hospitalized at UCLA for over seven months until he was discharged to an Illinois foster home on October 4, '92. Throughout his hospitalization our visits were monitored. During those seven months he was admitted to the Neuropsychiatric Institute on April 21st due to the false diagnosis that Jeffrey was a victim of Munchausen.

Teaching funds were approved to support him during his MPI hospitalization. The psychiatrist who diagnosed Munchausen Syndrome by Proxy happened to be on tap to be an expert for the American Psychiatric Association involving Munchausen. Despite relentless diarrhea Jeffrey remained in the Neuropsychiatric Institute. His health deteriorated so severely that an emergency admission back into the medical center was necessary. A court order was granted to accomplish the transfer on July 30th. It is what happened to Jeffrey after he was transferred back into the medical center that is the focus of this report.

Beginning July 30th cyclosporin was started intravenously. Cyclosporin is a medicine which in 1983 has received FDA approval with specific labels for use. It is used to prevent organ transplant rejection.

Questions come to mind as to why Jeffrey would become so seriously ill while hospitalized at a major medical center. The first encounter with serious illness at UCLA occurred shortly after his admission. He suffered an electrolyte imbalance after his regular medications were stopped and his previous gastroenterologist's orders to avoid dairy products were ignored.

His second encounter with serious illness was during his hospitalization in the Neuropsychiatric Institute. Although he was taking numerous medications for his bowel disease the psychiatrist, the one aiming to be the expert, was his primary physician. Did his treatment play a role in his declining health? Was Jeffrey at risk the moment our parental rights to make informed decisions regarding his health care were temporarily taken from us? Did that legal situation open the door for the accusing physicians to benefit from

research related to the "treatment" of Jeffrey's unique and challenging medical problems?

On the surface the use of cyclosporin appears to be for treatment but was it used solely for treatment or was it used in part for research? Do medical articles written in 1994 by the accusing physician and another treating physician discussing the use of cyclosporin for their pediatric patients afflicted with Crohn's disease prove that their intent in using this drug was at least partly for research?

Since cyclosporin's initial FDA approval in 1983 it has still not been approved for the treatment of inflammatory bowel disease. The literature is filled with medical risks that discuss the serious risk factors associated with its use. Significant toxicity including renal dysfunction and super infections can result from the use of cyclosporin.

The accusing doctor and another pediatric gastroenterologist treating physician state in their article published in 1994 that cyclosporin benefits less than 25 percent of the cases of ulcerative colitis or Crohn's disease. Did those doctors misuse our legal system to obtain those statistics? Was Jeffrey part of that research?

Today Jeffrey carries three diagnoses. The University of Chicago diagnosed Crohn's disease during November '96. Although UCLA initially diagnosed Crohn's disease during February '92 at the latter part of Jeffrey's seven month hospitalization his physicians committed only to his symptoms being consistent with Crohn's disease.

Jeffrey also has asthma the University of Chicago diagnosed and is treating it.

A Mayo Clinic geneticist diagnosed Jeffrey with a rare genetic condition which is described as a variant of the Johanson Blizzard Syndrome.

Given Jeffrey's unique and complex medical status was enough known in 1992 about how cyclosporin would affect Jeffrey's future to warrant its use? Was Jeffrey really a victim of research which was masqueraded as treatment? In trying to answer that question only more questions come to mind.

Why was Jeffrey's NPI hospitalization, which lasted for over three months, covered by teaching funds? But most puzzling is why didn't UCLA provide Jeffrey's insurance carrier with complete medical records so that their physicians could review those records? Also the entire claim for Jeffrey's seven-month hospitalization was denied in October 1992 because the insurance carrier was not given the requested records. To this date the claim remains denied.

In legal situations where parental rights have been temporarily taken away is research disguised as treatment being conducted on innocent precious children?

Thank you.

DR. CHILDRESS: Ms. Neason, the commission thanks you

and also Jeffrey for sharing your story with us today.

MS. NEASON: Thank you.

DR. CHILDRESS: Alex?

MR. CAPRON: I would like you just to clarify this term that you are using, "teaching funds." By that do you mean simply UCLA funds that are not reimburse from outside?

MS. NEASON: All I can tell you is there is a medical record written by the accusing psychiatrist which states that he went to the Director of the Neuropsychiatric Institute requesting the use of teaching funds for Jeffrey's care to support him and it was granted.

MR. CAPRON: Thank you.

DR. CHILDRESS: Thank you very much for joining us today and you, too, Jeffrey.

MR. NEASON: You are welcome.

DR. CHILDRESS: We will take one more person before the break and we will take a truncated break which we have earned by virtue of running overtime.

Is Ms. Shalmah Lee Prince here?

Ms. Prince, thank you for providing written testimony to us.

MS. PRINCE: My name is Shalmah Lee Prince and I am here today with my husband who has taken his vacation and we have driven about 500 miles from Cincinnati to be here today.

This is hard. Okay. It is very, very hard to do this because I was used in research with 309 other people whose names I have with me but they are not here and you have families and it is unfortunate that people whose mothers and fathers have come and done and tried to fight for them and speak for them because it is very hard to say I have a mental illness and I was used in experiments and something was wrong. No one believes you. You have no credibility at all. None. And it makes us perfect research subjects. We have no credibility.

I have bipolar illness and the owner of the Washington Post has come out and said that her husband had manic depression and committed suicide as a result. I am not dumb. I am not imperceptive. All throughout my medical records it says patient very, very insightful. But I never ever, ever suspected that I had been set aside as a research subject in the unit that I was in with primarily Black patients, two Whites all times and ten Blacks at all times, locked in 24 hours a day, not allowed out. My mother could not get me out. I could not get out.

But it is treatment. "She is very, very sick. She is so, so sick." And it was experiments, being genetically reengineered, being washed out, being given a combination of psychotic drugs that created psychosis, induced psychosis. They had the right combination for the design of their study. We were totally abstracts. We were not persons. We were not talked to. We were not looked at. We were given no therapy. None. Psychotherapy

has been shown to work. I heard Mr. Temple say here this morning. Yes, talking to people really helps. It is really effective.

For 45 minutes every Friday we were taken to the little room and said, "You are really angry at your mother, aren't you? You are really angry at your father, aren't you?" We felt so bad. We felt so bad. There had to be some reason why we felt so bad but we did not know why.

So for ten years I thought what happened to me in there, what happened in there, I was in leather restraints for three days, four point leather restraints, while people were invited in to watch me and to look at me and my behaviors were recorded every 15 minutes. My sleeping. My eating. My hostility. My choreic movements.

Huntington's disease was part of the study.

I cannot believe that NIMH authorizes this. Have I written a person of the state? Yes, the head that evaluates these programs and okays them for Medicaid said they were fine.

I would like to read what each doctor said the risk of a washout is and, yes, washouts are terribly dangerous. You are never the same again on lithium if you are taken off cold turkey which I was and billed $30,000 for the experiment.

Dr. Garver, the lead researcher now at the Dallas VA, was asked about patient risk in a sworn deposition and he said, "They might have a delusion and act in irresponsible ways so as to harm themselves or someone else." He went on to say, "Well, conceivably some patients because of delay in initiation of medication would have a delusion they were capable of flying out a window and injure themselves." I guess they would, wouldn't they?

I guess they were not surprised when a male patient beat me up or when I took a table and tried to throw against a window to get out, or when I took an overdose of medications after going home.

Dr. Jack Hirschowitz (?), the unit chief now at Mt. Sinai and the Bronx VA, stated in his sworn deposition, "The risk of a drug free washout period for any psychiatric patient would be that their illness is not being treated so that as a result they could potentially harm themselves or potentially their illness could get worse."

I want to know one thing. Where are the Black people in this room today? That is who is primarily being used in Cincinnati and they do not even know it.

Martin Nemolar (?), a protestant minister imprisoned during the German's dehumanization movement, said the following: "They took the socialists. I was not a socialist so I did not speak. They took the union tradesmen but I was not a union tradesman so I did not speak. They took the Jews but I was not a Jew so I did not speak. And they started to take me away and there was no one left to speak for me."

Well, there are people here speaking today and I cannot tell you the effort it took for them to get here or how hard it is

to talk about being decisionally impaired particularly when it is your child.

Please listen and please do not say you cannot do anything about this. This is terrible what is happening. It is terrible.

Thank you.

DR. CHILDRESS: Ms. Prince, we thank you very much for sharing that story. We know how painful it was.

Are there any questions?

MS. PRINCE: Well, I would like to answer the question that is not going to be asked and that is what would help the psychiatric patient with the enforcement of regulations.

People may have psychiatric diagnosis but they do know when something wrong is happening. The problem is people do not believe them and there is no one to tell. I have written OPRR and it is very difficult to sit down and type a credible letter to OPRR. For the normal person who is used in this kind of research they cannot do it. So it is a closed circuit. It is a dead end street. You are not going to hear about the abuses because the people that are being abused that know they are being abused and even suspect the type of abuse that is going on have no one to tell and no way to tell it.

I mean if I had been given a card when I left that unit that any federally funded research, any NIMH, any NIH research, that each person has to be given a card with an 800 number, if you feel in any way that this research was not helpful to you, if there was abuses of any kind, please call this number. Because it is the patients that know and it is the patients that can speak up. It is just that no one believes us.

Thank you.

DR. CHILDRESS: Thank you. Trish?

DR. BACKLAR: This is not a question but I would like to confirm what you just said. Many people when they are psychotic know who is being kind to them.

MS. PRINCE: Right.

DR. CHILDRESS: Thank you again.

We will reassemble in seven minutes at 25 to 11:00. We earned a break but not a long one.

(Whereupon, a break was taken.)

DR. CHILDRESS: Our next speaker will be Stephen Post, Professor Stephen Post, representing the Alzheimer's Association.

For members of the commission he has made -- given us one copy of some materials. Those will be copied and distributed to the commission.

Stephen, I am not sure you were hear earlier. We are asking everyone to limit it to five minutes so we will have time for questions.

DR. S. POST: That is fine.

The chair of the National Bioethics Advisory Commission,

Dr. Shapiro, wrote the Alzheimer's Association National Public Policy Office inviting testimony on research ethics involving subjects who are decisionally impaired. In response, the leadership of the association requested that I represent the association before you today.

The Alzheimer's Association and its network of over 200 chapters and 35,000 volunteers is the only voluntary health organization dedicated to research to conquer Alzheimer's disease and to providing support and assistance to people with the disease, their families and care givers.

Educating and informing the public and care professionals on ethical issues is one of the principle tasks of the association. Toward this end the association established several years ago a National Ethics Advisory Panel on which I have been honored to serve. With the guidance of panel member, Dr. Greg Sachs, this group has discussed research ethics in people with AD in great depth on numerous occasions and has issued a formal document entitled Ethical Issues in Dementia Research, which was approved by the association's board of directors in Chicago on May 18th, 1997, and I believe has been disseminated to all the association chapters as well as to this committee.

This document which then you have before you should be understood as an important contribution to the national debate on the issue, both because of its content and because of its source. It is not an end to discussion but it is a step forward. It attempts to balance the association's powerful commitment to delay prevention or cure of this horrible dementing disease which afflicts four million Americans directly and another 19 million as care givers with reasonable but not excessive protection for research subjects. Please consider it with care.

Because of limits in time I wish to highlight the three major paragraphs on categories of research and then offer some interpretation of these paragraphs based on lengthy panel discussions to which I was privy.

Category A: "For minimal risk research all individuals should be allowed to enroll even if there is no potential benefit to the individual. In the absence of an advanced directive proxy consent is acceptable."

Category B: "For greater than minimal risk research and if there is a reasonable potential for benefit to the individual the enrollment of all individuals with AD is allowable based on proxy consent. The proxy's consent can be based on either a research specific advanced directive or the proxy's judgment of the individual's best interests."

Category C: "For greater than minimal risk research and if there is no reasonable potential for benefit to the individual only those individuals who (1) are capable of giving their own informed consent or (2) have executed a research specific advanced directive are allowed to participate. In either case a proxy must

be available to monitor the individual's involvement in the research. Note: This provision means that individuals who are not capable of making their own decisions about research participation and have not executed an advanced directive or do not have a proxy to monitor their participation cannot participate in this category of research."

Now as for the background discussion, which I think will help you interpret this, the conversations of the Ethics Advisory Panel indicate a wide definition in Category B of reasonable potential for benefit to the individual. The many new antidementia compounds under investigation would categorically be of reasonable potential benefit as would nearly all other current investigations. Thus the association endorses the proxy consent process currently in place in all the Alzheimer's disease research centers across the United States.

The ravaging nature of Alzheimer's disease, the strong desire of the association's grassroots constituency to make scientific advances, and the threat of AD to the well-being of millions and millions of people in our aging societies can permit nothing less. To quote the title of the association's 1996 annual meeting program, "A world without Alzheimer's."

But the association's document is highly protective of research subjects under Item C, that is in the clearly nontherapeutic context. Conversations of the Ethics Advisory Panel indicate that the research specific advance directive must include documentation of an explicit desire to participate in research beyond minimal risk that holds no potential to benefit the individual subject.

Further the panel and the association believe that for a considerable period of time after diagnosis people with AD ought to retain their capacity to complete such an advanced directive. The panel noted that there are many expressions of profound altruism in which individuals with the disease indicate an explicit desire to contribute to an eventual cure of AD for the benefit of future generations. Genetic risk factors suggest a concern for their children.

The association's position in Item C then is protective but it does not preclude such forms of altruism so long as informed consent is ensured. Monitoring by a proxy provides a fail safe mechanism consistent with comfort and dignity.

This document does not address the possibility of distinguishing between degrees of increase over minimal risk as the proposed Maryland legislation does but there is nothing in the association document inconsistent with efforts to define several levels of risk.

It should also be noted in the context of an irreversible and progressive dementing disease such as Alzheimer's family members eventually make decisions for their loved ones in all realms of life. The care of people with AD depends on trust and the

association, which includes millions of care givers, has confidence in them.

On behalf of the association thank you for your kind consideration. The association and its Ethics Advisory Panel looks forward to close rapport with the National Bioethics Advisory Commission. AD has been called by Louis Thomas the disease of the century. Historian Arnold Toynbee said forty years ago that at the close of the century the greatest moral problem would not be death but the death of the mind before the death of the body.

No condition of severe mental dementia impacts on the present and the future as much as this one.

Thank you.

DR. CHILDRESS: Thank you.

Yes, Bernie?

DR. LO: I want to ask you a question about research advance directives. How feasible are they? Do you have a feeling for what percentage of Alzheimer's patients complete them. I want to put that in the context of the really disappointing response of the public at large to advance directives for their own medical treatment.

DR. S. POST: The use of research advance directives which occasionally occurs in the Alzheimer's population is by Dr. Sachs' acknowledgement extremely rare. This means, in fact, that in category C, clearly nontherapeutic research, the likelihood of an individual volunteering for such is really small. I think that is the subtext of this document if you will.

There have been remarkable cases, somewhat outlier cases, I have seen of individuals who consented to neurosurgery for research that held no therapeutic value to them personally and in one case an individual probably was harmed and wound up in a nursing home I think a year or two earlier than would otherwise have been the case. But I can only think of seven or eight of examples of that that I heard about anecdotally over the last five years. So these would be, if you want to call them, research groupies. They are an unusual breed and we view that Category C then as highly protective and is unlikely to be relevant to a great many individuals.

DR. LO: If I could just follow along, then is there an important research that would be foregone because of the impossibility of enrolling subjects for those kinds of studies?

DR. S. POST: I do not think so because the association, you know, you have to go to one of the association's board meetings to recognize, this association is hell bent on prevention or delay of the disease. The association's formal research policy statement is that if Alzheimer's disease could be delayed by five years it would effectively cut in half the number of people suffering from AD because they would die of other age related disorders before onset.

Almost anything you could imagine would be in Category B, that is to say potentially therapeutic, which raises some

questions that I am sure you may want to consider and you probably have considered. But most of the research is, in fact, right now in the area of antidementia compounds and the association board and the panel believes that these compounds categorically as I said earlier are of potential benefit to any subject.

DR. CHILDRESS: Thank you very much.

DR. S. POST: Thank you very much.

DR. CHILDRESS: Mrs. Beverly Post?

Thank you for joining us today.

MRS. B. POST: Thank you for having me.

I am Beverly Post, Highland, New York. When I lived in Maryland I was co-president of the Alliance for the Mentally Ill. I was co-president of the Alliance for the Mentally Ill of Anne Arundel County and it was at that time our son was a research subject at the Maryland Psychiatric Research Center.

He was there for two years. We had been led to believe that we would find answers for his unclear diagnosis. We know now he should have been excluded from being admitted because (1) he did not suffer from schizophrenia and (2) I had informed them of a previous severe reaction to haldol, which they said would have excluded him. I have just found that out.

He suffered more at Maryland Psychiatric Research Center than ever before or since. His condition deteriorated badly. Despite my warning he received haldol. It resulted in a dystonic reaction requiring emergency surgery intervention.

Against my vehement objections he was subjected to amphetamine to be administered intravenously on three different days. The third session was canceled due to his extreme reaction.

Spinal taps were also performed. Why? Spinal tap is quite painful, I know. I have had two for medical reasons.

Another test used Apo morphine injections causing bizarre behavior.

Growing up no one had ever hit our son but a staff member severely blackened his eye when he did not respond quickly enough to picking up books. I have his statement which was notarized of what happened at the time.

Asbestos was discovered in the building where the unit was located. After seven months of exposure to asbestos a previously condemned building was used. This was D cottage. Research was at a stand still and lacked facilities for protocols to be carried out.

It took me two years to get his records, to get those protocols, and I had to get a lawyer to help me do it. I did not know at the time what was going on.

It was while in D cottage that the male patients were illegally subjected to the humiliation and cruelty of what is called "Charm School." They were tied in chairs from 10:00 o'clock until 3:00 o'clock. Some more loosely than others. They were not able to leave the room. Lunch was brought in. No books. No music. No TV

or writing materials were allowed.

What was the purpose of this dehumanizing experience? Imagine if you can the effect on our son. He is musically gifted and he is a compulsive writer. I called the doctor twice to tell him that this was against Maryland law HB-1314 regarding restraints. I had lobbied to get that law passed. Ironically my son was now being illegally restrained. I was ignored.

I did not know what to do. Finally a consumer advocate who learned about the situation reported the abuse to Dr. Carpenter and the State's Patient's Rights Advisor who sent in the Spring Grove Rights Advisor on a surprise visit to investigate. An immediately stop was put to Charm School.

After they moved to the new quarters I was called in and told my son was being discharged. He was stable and then going out to a day program. Suddenly for no reason his medication was changed. He came apart at the seams. In a panic his low dose was tripled. I never found out why. Just that it was a team decision.

When we left MPRC he was broken physically and mentally. He had been exposed to and acquired a positive TB test there. He had been a nonsmoker when he entered. He left a chain smoker. He has developed an allergy to tobacco causing him to be rushed by ambulance to the hospital for treatment of severe bronchial spasm.

He is still bitter about his experience there.

He has now been correctly diagnosed at three different institutions, Johns Hopkins, University of North Carolina and Westchester Institute for Human Behavior. He is a high functioning artistic person. He receives services from the Developmentally Disabled Office.

It concerns me greatly that the animal activists can protect the lower forms of life from inhuman research but thus far little has been said about human guinea pigs.

This is an article, a study in which my son was used, published by the doctors at Maryland Research Center. Two years of his life were lost there. I will never get over my guilt for encouraging him to go there and for ignoring him when he wanted to tell me to go to another hospital.

Thank you for listening to me. I hope this will help in the future. I cannot help my son. The past is gone. But I hope maybe others can be helped with better regulations and monitoring. Research needs to be done. I know that. But it can be done differently.

DR. CHILDRESS: Thank you for sharing this important story and also for the recommendations you made.

Are there any comments or questions?

Alta?

MS. CHARO: Yes. Ms. Post, I am trying to understand how this can have happened. It is the second story we have heard now about the same facility. These questions may not be things that you can answer but do you know if this is a private facility or a

state facility or part of a university?

MS. POST: I am sorry. I cannot understand the question.

MS. CHARO: Is it that you cannot hear me or -- I am trying to understand what kind of institution this is? If it is private? If it is part of the state health department or if it is part of the University of Maryland?

MS. POST: Maryland Psychiatric Research Center at that time was under Maryland University but it was on the grounds of Spring Grove hospital so it would be served by Spring Grove hospital by the space they used, by the meals that were brought in. But, yes, it was the University of Maryland because Dr. Monroe at that time was head of everything. Dr. Talbot now holds that same position.

MS. CHARO: When your son was admitted to the unit were you under -- did you have the understanding he was being admitted for therapeutic treatment or as part of a research protocol?

MS. POST: My understanding was we do not have a clear diagnosis. Here he will get PET scans and MRI's. We will do all kinds of testing and we will maybe even give him a trial of new medications. Nothing helped him. Nothing will have helped because he is artistic. He is not schizophrenic. He is a bipolar. I did not know that then. I know it now.

MS. CHARO: Thank you.

DR. CHILDRESS: Thank you very much.

Our next speaker --

DR. BACKLAR: I am sorry, Jim.

DR. CHILDRESS: Sorry, Trisha.

DR. BACKLAR: I just wanted to make the point, this is not a question, that both Ms. Becker and Ms. Post made that at the time that you thought your son had schizophrenia and that both of you said that you felt very guilty about having done this.

I think one of the issues that we do not address here but we will be taking into account in terms of families and care givers is that often people do not know what to do when they have a relative who has a serious mental disorder and attempt to find care in a research protocol.

DR. CHILDRESS: Thank you, Trisha.

Ms. Maggie Scheie-Lurie?

Is she here?

You are representing the National Alliance of Mentally Ill, is that correct?

MS. SCHEIE-LURIE: That is correct.

Dr. Childress and members of the subcommittee, my name is Maggie Scheie-Lurie and I am the consumer outreach coordinator for the National Alliance for the Mentally Ill. NAMI is the nation's largest grassroots organization representing persons with severe mental illnesses and their families.

Research represents the best hope we have for

alleviating the suffering caused by severe mental illnesses such as schizophrenia, depression, bipolar disorder, obsessive compulsive disorder, and anxiety disorder.

Remarkable advances, which have already occurred in treating these disorders, would not have happened without the participation of people with these brain disorders as human research -- human subjects in research.

I appear before you today as someone who has participated for many years as an outpatient human subject in a longitudinal clinical protocol on clinical depression at the National Institute of Mental Health. My experience in this protocol has generally been quite positive. Throughout my participation I have had access to medication and clinical treatments which have for the most part been successful in controlling the worst symptoms of my illness. Additionally, I have usually been treated in a respectful and dignified manner by the research investigators and staff persons.

These people have communicated to me the nature, goals, risks and benefits of the research in an understandable manner so that I have been able to consent in an informed manner to participate in specific aspects of the study.

But I am aware that there are many individuals who participate in research who do not benefit directly from their participation. Some research protocols are not designed to benefit individual participants. Even potentially beneficial research designs sometimes involve procedures which are painful or risky for individuals participating as human subjects.

Some research participants may actually experience psychiatric relapse or deterioration, particularly those studies involving relapse study, drug washout procedures or placebo controls.

At the same time some individuals with severe mental illnesses who participate in research may lack capacity at times to understand research and to consent to their participation.

While it is vital for people with severe mental illnesses to participate in research clearly procedures must be established to protect the well-being of these vulnerable consumers.

In February of 1995 the NAMI board of directors adopted policies which contain specific recommendations of this nature. These recommendations were developed through a sensitive consultation with consumers, family members, researchers and other experts. NAMI's recommendations attempt to strike a balance between the importance of research with the equal importance of protecting the well-being of people who participate in the research.

In the short time remaining I will focus briefly on four aspects of these recommendations. Our complete NAMI policy is attached to our written testimony.

Number 1: "Informed consent." Informed consent should

be an ongoing process designed to ensure that consumers who participate as human subjects in research understand as much as possible the objectives, procedures, risks and benefits of the research. Researchers must be particularly sensitive to changes in functioning and comprehension which may occur during the course of a research protocol and must make special efforts to provide information to consumers and their families during periods when symptoms may be exacerbated. Researchers should also be sure to inform subjects and their families of potential alternatives to research.

Number 2: "Assessing capacity." Some important research, particularly research on experimental medications, may require the participation of individuals whose symptoms are quite severe. In research of this nature it is important to carefully evaluate the capacity of these individuals to comprehend the research and to provide informed consent to participate in the research. We strongly believe that responsibility for assessing capacity should be vested with a qualified individual who is not directly involved with the research.

If it is determined that a person lacks capacity to provide informed consent substitute consent should be sought from a family member or others who are legally entrusted to act on behalf of the incapacitated individual. The responsibility of research to provide clear and comprehensive information to research participants exists even when these individuals lack capacity to provide informed consent. Research investigators should make all efforts to inform these individuals that they are participating in research and to ensure that these individuals agree to such participation.

Number 3: "The important role of IRB's." IRB's have very broad responsibilities to evaluate and provide oversight over research protocols. However, there are no requirements that IRB's monitoring research on severe mental illnesses include members with direct and personal experience with these disorders. There are also no requirements that members of the IRB make themselves known or are available to the individual research participants. We have three recommendations to remedy these problems.

First, all IRB's evaluating research using human subjects with severe mental illnesses should include consumers and family members.

Second, IRB's should receive specialized training about severe mental illnesses and the needs of people who suffer from these disorders.

Finally, IRB's should designate at least one person who will function as a point of contact for individual research subjects and should be sure to inform research participants about this person.

Four, research using placebo controls. The administration of placebo to individuals with severe mental illnesses participating as human subjects research on experimental

treatments can cause relapse and immense suffering. Consequently we hope that the day will soon come when valid research can be done without the use of placebo controls. In the mean time we strongly believe that all individuals should be given trials on experimental occasions even if they are initially included in the group which is administered placebo.

In conclusion, NAMI supports the critical need for biomedical research on severe mental illnesses. At the same time we recognize the importance of establishing strengthened procedures for protecting the health and welfare of vulnerable individuals participating as human subjects in this research. Through open dialogue and willing consumers, families, members of the scientific community and others, we believe that consensus can be reached on how this balance can best be achieved.

I greatly appreciate this opportunity to testify before you.

Thank you.

DR. CHILDRESS: Thank you. Thank you for strictly respecting the five minute limit.

Trish?

DR. BACKLAR: I am interested in the remark that you made in research using placebo controls in which you say in the meantime we strongly believe that all individuals should be given trials on it, et cetera, et cetera.

Could you talk a little bit more about this? Do you really mean all individuals?

MS. SCHEIE-LURIE: What I am saying is what the policy means to say is that individuals who have been in a research study in which they were given a placebo and were not given the benefit of the medication being studied should be allowed to have access that medication following the study if they choose.

DR. BACKLAR: I think that we both read this quite differently. I thought that you were saying that all individuals should be included in a trial in which there was a placebo arm.

MS. SCHEIE-LURIE: Well, again -- well, I believe this is saying that many individuals, I believe, go into research believing that they will personally benefit. If they, in fact, end up in a placebo group instead of the group that receives the medication being studied they are not having the opportunity to receive a benefit of that research medication. I think what this is saying is that they should be given the opportunity following the study to perhaps benefit from that medication.

DR. CHILDRESS: Alex?

MR. CAPRON: Two things. One is to follow up on your exchange.

Trish, if you look at point nine in their recommendations I think it is stated a little more clearly. It is right after the testimony.

DR. BACKLAR: Oh, yes.

MR. CAPRON: The question I had was about your second suggestion for IRB's that they should receive specialized training about severe mental illnesses and the needs of people who suffer from these disorders. Do you have in mind a model in which this has been done where you would be able or we would be able to see what such education or training consisted of and what effects it had on the IRB's functioning?

MS. SCHEIE-LURIE: I am not aware that we have a model at this point that has been used but I am sure we would be more than happy to be involved in the development of such a model.

MR. CAPRON: Without the existing model can you enumerate some of the sorts of things that such training would address?

MS. SCHEIE-LURIE: Well, I would think the basic nature of these disorders, the typical kinds of treatments that people receive, the difficulties that people may inherently experience in the course of treatment and in the course of attempting to recover these disorders. I am obviously talking off the top of my head but I think part of the problem is that the nature of what these illnesses are like is not necessarily understood by people involved in evaluating whether particular research protocols are appropriate.

Mental illnesses are not like other illnesses and I think it is really important that people involved in determining whether research protocols are appropriate know what the severe -- for instance, the ideas of washout periods. People knowledgeable about mental illness will know how devastating that kind of a period would be. So I think if an IRB was knowledgeable of the devastation that can occur and how someone's whole life can be destroyed in the course of a washout period it would be much more sensitive to the appropriateness of that kind of research protocol.

DR. CHILDRESS: We will take one more question.

DR. BRITO: Earlier this morning I kept hearing a recurrent theme and in a lot of the reading that we have received that keeps coming up about the suggestion to have an autonomous doctor or someone outside of the research, whatever research protocol, to help that patient.

I was curious given your positive experience how did you get involved in research in the first place? Were you referred by someone? Did you have someone guiding you through that that was not involved in the research?

MS. SCHEIE-LURIE: I initially became involved in this research because I was seeking treatment. I sought treatment at a local community health center which was not able to serve my needs and they said, "We cannot do this but it is possible that you will fit the protocol in this particular study at the NIMH," and I was evaluated and I did fit.

I have been fortunate that the people I have been involved with all along have been sensitive and responsive to my

questions about what is going on, why are you doing this, what can I expect to learn from this, what can you expect to learn from this, how can I benefit. I have been very fortunate. I have been unusual, I believe, especially in the course of hearing what we have heard today and what I have known from talking with people outside of this hearing, that many people do not experience that. I consider myself something of an anomaly.

DR. BRITO: But when you say the people that you have been involved you are talking about certain people in the research program. Once you were referred you had no further contact with another physician outside of that program?

MS. SCHEIE-LURIE: No, I did not.

DR. BRITO: Okay.

DR. CHILDRESS: Thank you again.

MS. SCHEIE-LURIE: Thank you.

DR. CHILDRESS: Before we turn to the last person who is on the list that you received let me just note that I have in addition to Ms. Vera Sharav, Dr. Guha, Dr. Buchov and Mr. Brownstein and parents. If I omitted anyone who had given a name to the staff please let Pat Norris know.

Pat Norris has just informed me that those are interested in getting copies of the testimony please sign up on the sheet outside and copies will be available tomorrow afternoon.

All right. Ms. Vera Sharav?

MR. CAPRON: By testimony you mean just submitted statements?

DR. CHILDRESS: Yes. Thank you.

MR. CAPRON: Not the actual testimony.

DR. CHILDRESS: Not the oral testimony, right.

MR. CAPRON: Which will not be transcribed for a week.

DR. CHILDRESS: That is right. Thank you for the clarification.

MS. SHARAV: My name is Vera Hassner Sharav. I am cofounder and director of Citizens for Responsible Care in Psychiatry and Research. It is an independent network of concerned citizens, families and patients.

The speaker before me admitted that she was an anomaly of what the correct procedures for using a human subject ought to be in psychiatric research. I am here to discuss the vast majority.

The families, in fact, that we have brought before you are victims of therapeutic neglect, betrayal of trust, and institutional deception. Their children and countless others who remain silent became unwitting martyrs for science in experiments which caused them profound harm. They went to research because they had been cast out of the health care system. They have very few options and so they looked to research instead.

Overall, neglect and poor treatment outcomes are, in fact, the norm in psychiatric treatment and in research. The two go hand in hand. But when information about the risks of relapse are

withheld from patients and their families the consents obtained from them are anything but informed.

In a court deposition a senior researcher at a major VA hospital in New York stated, and I quote, "I have had occasion to review many consent forms for psychiatric studies during the late '70s and '80s. I can state that I have seen not one single consent form during that period of time that discussed any risks associated with the drug free period or the withdrawal of medication. It was the norm and practice of researchers and IRB's not to discuss any such risk in consent forms even though the risk of increased symptomatology is a possibility."

Thousands of uncomprehending patients, who lack protections, are recruited into pharmaceutical sponsored drug trials in which their welfare is sacrificed to speed up the testing process. Abrupt washouts are a way of speeding up the process. They do not have to be done that way.

They are also fair game for speculative experiments which deliberately provoke paranoid delusions, hallucinations, violent mania, disorganized thinking. University physicians are actually injecting schizophrenia patients with amphetamine, L-dopa, cocaine, apomorphine and PCP, especially at VA hospitals. They are deliberately inducing relapses so that their symptoms could be recorded. I do not know of another medical condition in which that kind of experimentation takes place.

In two recent experiments at the Maryland Psychiatric Research Center fourteen patients were subjected to PCP induced relapses. It is in a published document which you have a reference to. We believe that such experiments are inhumane and unethical.

Chimpanzees are protected from such experimental abuse but disabled human beings are not. The researchers' rationale for doing these kind of studies often defies logic as well as moral responsibility.

"Because of the psychotic like symptoms shown by depressed patients during treatment with L-dopa as well as reports of such symptoms in patients with Parkinson's we decided to try the drug in schizophrenics."

We come to you to tell you that human experimentation on mentally disabled patient is out of control. There are no limits. No independent oversight. No accountability for the human casualties.

Government agencies that are entrusted to be our guardians are authorizing experiments that deliberately exacerbate incapacitating illnesses. The FDA, NIMH and Institutional Review Boards are failing to meet their public responsibility. Instead they are serving the interest of the drug industry.

Let's talk about money. No one has mentioned this in the entire morning. U.S. sales for psychotropic drugs has doubled in five years. It is now $7 billion dollars. More than 10,000 clinical testing sites are competing for human subjects. There is a

race to test new drugs. Academic centers provide what industry calls a credibility bridge, prestige.

The fact is that conflicts of interest have compromised patient care and clinical practice. Psychiatrists have become partners with industry receiving thousands of dollars per patient to seed the market, that is called prescribing a drug, and to conduct drug trial studies. Academic researchers affiliated with state and VA hospitals earn as much as $20 to $30,000 per human subject in a drug trial study for Alzheimer's and schizophrenia.

Physicians are also setting up clinics and recruiting a stable of human guinea pigs whom they use repeatedly in drug trials. The FDA accepts unethically obtained data even when the human subjects are abused. They do not consider that a factor in how the data was obtained for premarketing.

The absence of protections has led to widespread violations. These are not isolated incidents. We need a national human subject welfare act that will provide all Americans with at least the protections mandated for chimpanzees. Those who profit from the drug industry claim that by providing safeguards for human subjects important research and scientific advancement will come to a halt. Well, that is nonsense. It will motivate research and industry to modify studies and the designs of the studies so that the welfare of the human subjects is not sacrificed for expediency.

Just as the Animal Welfare Act and its independent on site monitoring and oversight system did not stop genuine scientific investigation with animals neither will such scientific endeavors impede research where humans get equal protections. There would be enormous financial incentives. This enterprise is not going to come to an end.

Citizens for Responsible Care in Psychiatry and Research call for an immediate moratorium on nontherapeutic, high risk experimentation with mentally disabled persons who may be unable to comprehend or evaluate the likely or potential risks but who would suffer the consequences. Experiments which deliberately exacerbate psychotic symptoms should be absolutely prohibited.

DR. CHILDRESS: Thank you for your presentation.

Questions or comments from the commission?

MS. CHARO: You are obviously very educated about the range of regulatory protections that currently exist for human subjects and that would apply in the case of trials that are involving new drugs that the FDA is going to approve or taking place at VA centers. Yet despite those protections that are in place you are documenting problems that you have seen as unacceptable. I would like to understand more specifically exactly what kinds of changes you would advocate.

If I understood correctly, one is that you would advocate an absolute ban on research that is not expected to be a direct benefit to the particular subjects regardless of whether it has got a prospect for revealing information that will be useful for

people in the future; is that correct?

MS. SHARAV: When you are dealing with a group that by definition cannot truly comprehend and evaluate risks, yes.

MS. CHARO: And for those situations in which direct benefit is anticipated but which also has significant risks, okay, for which we currently have mechanisms like IRB's, are you suggesting a change in the composition of those IRB's or a change in the degree of authority that the IRB's have with additional authority granted to additional people? I would like to understand there what kind of suggestions you have.

MS. SHARAV: One of the things I would suggest, actually one of our positions is, is that we really would like to see a comprehensive investigation of current and previous practices to be conducted either by the Justice Department or the GAO. An independent evaluation so that what I have documented for you, you get the larger picture. You are aware of a GAO very preliminary report and even in that preliminary report they said, "There is no on site inspection." That is basic in animal research.

So the composition of IRB's, which you are asking about, sure if IRB's are to function and serve the public interest and protect the individual the composition has to change. The problem is there currently is no mechanism for accountability. You can have all sorts of written regulations, if nobody actually enforces them and if people who violate it or institutions who violate it are not held accountable they do not have much relevance.

What I am suggesting really, and I am sure you have been reading the press, and I have given you also an industry newsletter, this is where you find out that the pace is accelerated. The New York Court, which you are going to be talking about, the Appellate Division decision at the very end states exactly that. They recognize that this group is particularly in danger with this race to test because they are the ones who are available and no one is protecting them.

Others of us have means to ask questions, to get other opinions, to take that protocol to three other doctors and say, "Do you think this is worthwhile for me?" These patients have no option. They are being recruited in emergency rooms where they are in complete psychotic state. They will sign anything and it is being taken advantage of.

Indeed, some researchers are even regarding it as their moral obligation because they are not helping. Their moral obligation to become research subjects for society. Well, that is not what America is supposed to be about.

DR. CHILDRESS: Thank you very much. We appreciate your presentation and the discussion.

MR. CAPRON: Could I ask a question?

DR. CHILDRESS: Very quickly because, Alex, we have got others to get in this morning.

MR. CAPRON: I understand your answer. I just wanted to

have a clarification of your answer to the first question Ms. Charo asked.

You said it was because these patients, potential subjects, are unable to evaluate. Were you saying, in effect, those subjects who are unable should be governed by these across the board rules? Are you saying all subjects per se in all psychiatric research are unable?

MS. SHARAV: No. Ideally, and that is what we are really promoting, is a national act that would protect all human beings. The point is though the Americans with Disability Act requires making accommodations for a person's disability. Shouldn't the same be true here?

MR. CAPRON: Yes. I am not --

MS. SHARAV: In other words, the --

MR. CAPRON: There are people with types of cancer today who have no alternative treatment. They are sometimes asked to be in research which might have a potential benefit for them. They are sometimes asked to be in research which candidly holds no benefit for them where they are being asked to help scientists understand the tumor or the process, or something so that future patients might benefit.

They have the ability to consent to that.

MS. SHARAV: That is the difference.

MR. CAPRON: But that is my question. I mean, certainly to me some of the greatest tragedies we have heard about today were people who were successfully being treated with antipsychotic medications or other psychotropic drugs who at the time they went into the study it would seem to me were able to make the same kinds of decisions that the people who were talking -- my example of a woman or a man facing a cancer might make.

And I now understand your statement to be that you would say as to all those people, not just those who are in psychosis in an emergency room or those who are institutionalized and by a result of already being in the institution have constraints on their freedom to make choices, but these outpatient people who are, according to you, being recruited by psychiatrists in the community as a stable of people to be in their studies, none of them should be allowed to make choices? That we should have standards which we say, you know, this can be done or it cannot be done but you cannot consent to it even if you were willing.

MS. SHARAV: Part of the problem is that there is no true disclosure on the informed consent.

MR. CAPRON: There is no problem --

MS. SHARAV: Without that you do not even --

MR. CAPRON: You misunderstand. I am not arguing about consent. I just want you to clarify if you are saying that all psychiatric -- the recommendation of your group, I am trying to understand what we are hearing today, the recommendation of your group is that in all psychiatric research the subject is not capable

of giving consent?

MS. SHARAV: No, not all psychiatric. The scope of psychiatric patients is vast. We are talking about those who are schizophrenic or are in a bipolar episode. We are talking about people whose cognitive faculties are impaired in a major way. We are not talking about someone who let's say has depression and is on Prozac and can evaluate and is, in fact, leading a normal life and has access to the expertise and to the institutions that you and I do. We are talking about people who do not have access and who are being recruited.

DR. CHILDRESS: Thank you again.

Dr. Arun Guha?

Let me remind those who are speaking because of the shortness of time I have to enforce the five-minute rule very strictly.

Thank you for joining us today.

DR. GUHA: Thank you. My name is Arun Guha and I begin by applauding you for your decision to hold this public hearing because I believe that this is the only way that you can start getting a glimpse of the true problem which is enormous. You would not get it in the literature or interviewing hospital personnel or researchers themselves.

I am a little disappointed that you do not have investigative powers to follow through on some of those but I have a suggestion to make. You could ask each of the presenters for waiver of patient confidentiality and then interview some of the physicians. Most of them work for either NIMH or work for some NIMH funded government agency. If they refuse to talk to you that itself should be used.

The point I am making is that my experience shows and there are other experts who say that there is a conspiracy of silence in the medical community and there is no reason to believe that you will get true information from just talking to them.

My second suggestion is that you should think both tactically and strategically. By that I mean that the root cause of the problem is not just absence of regulations. In my particular example that I am going to tell you in a minute the regulations are there but they are simply ignored.

Vera mentioned that research subjects are recruited in emergency rooms. That is what happened to my son and I will come to that in a minute.

By strategic solutions I mean that you really should look at the root cause of the problem which is that in the medical community such unethical behavior is socially acceptable. When this happens everybody else knows it is happening. There is no protest from within the community itself to stop this. I have made a specific suggestion of how to handle the problem. It may not be the best one but I may not have time to discuss it. I would like to talk about that later on.

Let me now come to my case history. My son, age 26, died at the UCLA Neuropsychiatric hospital in November of '93. He had really no reason to be there. He was of sound body and sound mind with a Harvard MBA and a brilliant career.

He was in Kuala Lampur, Eurasia where he felt ill. He probably had a viral ill with a sore throat, difficulty in sleeping and so on. He was in a Hilton hotel and ordinarily when you are in an American hotel outside the country you still believe that you are getting the American standard of care. So he saw a center inside the hotel so he walked in and he was given five medications.

He reacted to one and he did not know anything about those medications at this time and if you like I can go into the details but I am trying to save time by not going into this now. He reacted to the one medication and he became delusional. Not psychotic but delusional because the medication was a dopamine blocker. So it does not fit the standard definition of psychosis followed by excess dopamine.

Unfortunately for him when he reached the United States on Thanksgiving Day I went down to Los Angeles and got him into the UCLA medical center. It was deserted. The only evaluation he got was from a first year resident who did not have his license to practice, wholly untrained and did not have supervision. As a matter of fact there was no attending physician for five days.

I have given you the documentation of an interview with the medical director of UCLA/LBI, who himself had agreed that my son's admission was never reviewed by an attending physician.

This untrained resident did not know what to do so he decided to put him on involuntary hold and put him as an inpatient. He could have cured him of his symptoms by a matter of hours by an antidote, by an antinergic (?) drug such as clozatine (?). That did not happen because nobody looked at him.

The next day when I went in I found him in a terrified state. What had happened he described to me is that somebody had been coming into his room at night flashing a flashlight on his eyes until he was supposed to open his eyes and then leaving. It was happening every 15 minutes. I did not believe him. I did not believe him. We did not think that this was possible and that it could be happening.

Later that evening a very senior nurse, the second highest ranking nurse, Janette Allen (?), told us that, yes, that is happening. That is the practice. That is the policy. I had a long debate with her about how could this be happening. How could this be policy? And she explained that this was clinical practice of this hospital in this unit. For four days I had been debating and arguing and pleading and begging with the residents and nurses that this does not make any sense. For four days both my son and I let them know it.

After his death on the fifth day on Monday we had an interview with Dr. Barry Guzay (?) who is the director of adult

psychiatric and in charge of the unit. He was in a state of shock himself because clearly he had not anticipated something like this happening. He answered many of our questions as if in a trance and I am sure that he was speaking mostly the truth. He did not have the mental state at that time to really think through and call up his answers.

We asked him about this night monitoring and he said, "Yes, standard procedure. A flashlight was shown in front of his eyes. Eye contact was made." He was the first person to use the word "eye contact" and we knew that what my son was describing was true. But even then we had believed falsely that it was part of the clinical protocol and we had been looking for a policy, clinical policy statement, from the hospital that says that and we did not find any. And we had expert opinion from the medical board and so on that there is no clinical reason for doing that and then we discovered that Dr. Guzay had been involved in sleep deprivation research. Apparently some psychiatrists still believe that that can be helpful to people with mental depression.

In our court filing that we have made under penalty of perjury we are accusing Dr. Guzay of conducting a totally clandestine research without even a shadow of informed consent which he conducted on my son.

And in terms of other comments that were made before I have run probably the most extensive letter writing campaign. We have gone to OPRR and when you talk about OPRR I hope the commission will look at the resources available to OPRR compared to the problem and the drug company monies and the NIMH funding, and some sort of a comparison to that.

Somebody talked about the attorney general.

DR. CHILDRESS: I will have to ask you to bring it to a close. We are --

DR. GUHA: Unless there are any questions I am done.

DR. CHILDRESS: Okay. Questions?

I take it in this particular case they would make an argument that this was clandestine research by a maverick investigator that had not gone through regular channels?

DR. GUHA: We believe that Dr. Barry Guzay had standard orders that anybody walking in and who was diagnosed with mental depression should be put under this protocol. The person who did that was totally untrained. He believed that he would get a pat on the back from his boss by doing so. And it was Thanksgiving weekend and there was nobody else available. I have provided documentation of most of this stuff.

DR. CHILDRESS: And we do appreciate the thorough report that we have. We have not -- we just received it this morning so we will look forward to reading it very carefully. Thank you for sharing it with us today.

MR. CAPRON: Are other people missing attachment 3 if you look back here? There is a page that says attachment 3 but

there is nothing after it.

DR. GUHA: I did it at 12:00 midnight last night so I might have --

MR. CAPRON: But if it is something you want us to see we may need to look at it.

DR. GUHA: I will send it in.

DR. CHILDRESS: Thank you.

Our next speaker will be Mr. Brownstein who will have five minutes and then his parents will have two to three minutes to add some comments.

MR. A. BROWNSTEIN: Good morning. My name is Andy Brownstein. I am representing myself. I have no recommendations. I have no answers. I just can speak about my own experience as a research patient.

What does it mean to be a research patient? I had no clue when I came to the NIH in September of '94. I have a pretty clear picture now. I really did not understand when I was desperate for help and came here and auditioned in front of a room filled with doctors and nurses and qualified and met the criteria to be a patient at the National Institute of Mental Health in the Biological Psychiatry Branch. I spent 13 months as an inpatient.

During my intake interview where my parents were present I was told I would spend three to six months here. After admission my nurse told me, "Three to six months? No way. The average stay was 12 months."

After spending a short amount of time on the unit I learned from patient colleagues that no one was there less than 12 months. Most were there at least a year-and-a-half to two years. My roommate was discharged after 26 months. My next door neighbor left after three years. My roommate said to me, "Deciding to come here was a very difficult and personal decision, and you will be sicker here than you have ever been before."

Somehow these lengthy stays were a secret at NIH. I met NIMH secretaries who were totally unaware that anyone spent that amount of time as an inpatient. When my three months came up I asked about discharge. When a shrug and a smile the doc was not sure. After six months I received the same response. Eventually I learned that I was, along with the others, in what they called an omnibus protocol.

As long as there was something of interest to the researchers that they could study and observe and as long as I was desperate and hopeful and willing to be poked and prodded, PET scanned, MRI, lumbar punctured, as long as there were fluids that they could collect I would be, as Kay Redfield Jamison of Johns Hopkins University said to me, "One of Bob Post's guinea pigs." Kay Jamison is a professor of psychiatry and she is a researcher at Johns Hopkins and a colleague of Dr. Post's who was the chief of the branch that I was in.

What does it mean to be a research patient? Someone who

is vulnerable. Someone who, like me, was desperate to find a cure. Someone whose community doc raises his hands in the air and says, "I do not know what else to do."

What is informed consent? Was I really informed when I signed all those long and complicated consent forms? I was very sick when I was admitted to NIMH. As a person with bipolar disorder refractory case, a case of ultra rapid cycling, out of control, depression so black I could not think or concentrate, often the smallest tasks, counting change, selecting items off the grocery store shelf, reading a map or a menu, making decisions was extraordinarily difficult.

On my first day in the unit the doc produced a black notebook filled three or four inches thick. It was filled with protocol consent forms. I was given no opportunity to read them, take them to my room, talk to my nurse about them, or consider them. The doc turned pages and I signed and I dated in triplicate.

At one point the doc said excitedly, "Oh, this one is really cool." Well, maybe not to patients. Other consents were signed en masse during group meetings. Minimal explanation was given. We signed, dated and the nurse would witness and sign. All of these without regard to our condition at the time or our ability to concentrate and read, and no opportunity to read and consider them. Consents were often signed months before a final version of the protocol would be approved by the IRB.

We were all blind to the protocols we were involved in or whether we were or were not on meds. From day one all of our pills were pink, active agents or placebo. You were unable to tell the difference between them. I signed this protocol October 31, 1994. A three-tiered protocol, two active drugs, and a placebo. The protocol I learned at my blind breaking began sometime in March of '95.

I was given a revised version of the protocol and had it signed on June 5, 1995. This was a three-tiered protocol. I was given the consent form for the second drug, I began this protocol in March, I was given the protocol for the second drug on June 5th, 1995. The protocol I was already in was three months -- I was already in it for three months.

The protocol was to be three arms of eight weeks each, March through July, and should have ended, and I should have been discharged. The protocol lasted eight months. I was discharged October 25, '95.

At my blind breaking I was shown pictures of my PET scans. My doc was excited to show me the difference between depressed periods and times when there was greater activation in my brain. He told me the images of those depressions were during the lengthy period when I was not receiving an active agent.

The placebo periods were horrible. All of the patients were apprehensive and scared knowing placebo periods were built into the protocols. During my 13 months I was in placebo phases a total

of 14 weeks. No effort was made by NIMH to assist me in finding a doc on the outside in the Philadelphia area where I live who could or would take on a complicated case like mine with a cocktail of meds that included drugs that were not approved by the FDA for the treatment of bipolar disorder.

It was very difficult finding a doc in a city with five medical schools especially after knowing I had been a patient at NIMH. No follow-up, no phone calls, a cold discharge.

At my last group meeting the docs, nurses, patients, my good-bye, I was told by my doc with a smile, and he was laughing, and he was excited, I had broken the record for the number of procedures done to patients on that unit during my time at NIH.

On the day of discharge I met Bob Post, my branch chief, on the sidewalk in front of building 10. He was waiting for a bus. He said, "Thanks for your time and for all the body fluids you have provided us. Good luck. Oh, by the way, what are you going to be doing?"

I learned a lot while I was at NIH. I had a respect for research but I would not recommend it to anybody. Research is cold and research subjects are treated with much less respect than so-called healthy normal volunteers. I still get nervous when I exit 495 and drive down Wisconsin Avenue towards NIH.

Thank you.

DR. CHILDRESS: Thank you for your powerful story. Could you just add a couple of minutes? The Brownsteins have also indicated they will provide written testimony. They were not aware that was an option and they will later provide written testimony for us.

MR. M. BROWNSTEIN: I am Mel Brownstein, Andy's father, and I want to address just one point and that is confidentiality. Whether we speak of research or treatment when dealing with mental illness we are dealing with the whole family, that is the impact of the illness on the family as a whole requires -- we reexamine some of the meanings and the function of confidentiality.

For the entire 13 months that Andy was at NIMH no one, neither the doctors or the social workers or the nurses, ever contacted either my wife or myself to share how Andy was faring. No one opened the door to acknowledge that we were concerned and that we were part of the illness. If the three or four extended furloughs that Andy got, and they would receive furlough to go home for 14 or more days, our son came home and no one contacted us after that for a debriefing. How did it go? How did he fair? How did you respond? How was his interaction with family, et cetera? Not one time. And there was no support for that.

Nor have they made any effort after discharge to follow up with the patient or the family. No one from that institution, from that ward, has ever called Andy or us to say, "How is he doing? What is happening?" To me this is a total disregard for either the well-being or the progress, or the state of the patient, or the

family.

Confidentiality implies -- and I was a professor of social work for many years so I dealt with this. I tried to teach it. But confidentiality implies that the treater will not misuse the information gleamed from the treatee, from the person being treated. That is what is shared is not grist for a rumor mill. But it does not mean that the treater cloaks him or herself in silence or distance from intentionally -- from intimately concerned parties who, in fact, play a role in the care and concern of a patient long after the treater is gone.

Andy is home now for almost a year-and-a-half, two years. We are the caretaker. We are concerned. We see the depths of the depression my son is going through. We see that this is a life unborn.

These people who have taken his fluid have never made any contact or any effort to reach him or us to say what is happening. What is the product of what we have done? This silence and distance seriously negate any accountability on the part of all those who are involved. No one should have that kind of power. And particularly where there is such vulnerability that control has been ceded to them, where trust is a prerequisite, or prerequisite for a positive outcome of this illness.

I thank you for the opportunity of talking to you. I appreciate what research is but these people were damn cruel.

DR. CHILDRESS: Are there questions to be directed to -- and Mrs. Brownstein, too, will be available for questions. So are there questions directed to the Brownsteins?

MS. CHARO: Just, Jim, one.

MR. CAPRON: Use your mike, please.

MS. CHARO: Yes. Can you help me understand why you went into this protocol to begin with? What led you to do it and what you expected? And in the course of it as you discovered that it was perhaps different from your expectations whether you ever considered leaving and, if so, how that went?

MR. A. BROWNSTEIN: It is a complicated question and the answers are very complicated. I went in because I was really sick and I was -- meds just were not working and I had -- when I entered NIH -- I began to be sick in junior high. By '81 I was 21 and I was finally diagnosed. The doctor said as a teenager this is very difficult to make a diagnosis. The first hospitalization was in '81. Meds just did not work. I was on lithium for eight, or nine, or ten years. It just did not work. A whole variety. You go through the list and I was on everything in combinations for lengthy trials, retrials, so on.

I got a good doc at Temple University. He was the chief resident. He was terrific. I loved him. The best doc I ever had.

I got to a point after -- I guess it was almost two years of working with him when he just said, "This is just beyond me. We have tried, you know, and my own feelings deep in my heart

is that there is nothing more I could do. I would be lying to you. There is nothing more that I know how to deal with."

At that point, you know, looking through books and magazines I discovered the name NIH. I had never heard of it. I talked to him about it and he said, "Good idea." I made contact. The papers were faxed. All the records were faxed. I was invited for the interview. That was the reason that I came is because I just ran out of choices and I was desperate. I mean throughout all that I just did not give up. I was close but I did not give up and we came here.

I do not understand what research is. I am not a scientist. I am a layperson. I did not understand what it meant. When you finally get here and you are here for a period of time and you begin to understand that all of this is blinded, you do not know what you are on, the nurses do not know what you are on, the doctors do not know what you are on, everything is in code number, you do not know when you are on something, when you are off something.

And at some point you begin to understand that this blind breaking which they kind of held in front of you like a carrot, it was the important day when we would find everything out, at some point you realize you cannot leave. You cannot leave because until you know that a protocol is completed, which is the blind breaking, if you are desperate for help you cannot leave. You have got to wait until the end.

MS. CHARO: Thank you.

DR. CHILDRESS: Would one of you like to add something to that and then we will have to go to our last speaker of the morning.

MRS. BROWNSTEIN: Unless there are other questions I would just say that --

DR. CHILDRESS: Could you go to the microphone?

MRS. BROWNSTEIN: Good morning. I am so glad you are attending to this problem. You are facing a parent who has for many years been desperate trying to help a child who obviously is articulate, capable, in control, a socially very acceptable person, who tried very desperately to make his life better. I cannot tell you how many times I have scoured the house since he was in junior high school for items which might indicate that he is trying to take his life because his bottom line is suicidal ideations. He prepares.

So our first episode was to see a collection of pills and we intervened with that. We found a gun, which we intervened. Now I look for items that might indicate that -- the cars also will be locked so that he cannot run the car. All of those things. So we live with that. We live with a constant condition of trying to be human and sociable and a terrible fear, my feet get cold, the terrible fear that we will find our son dead.

So these -- mental illness we have learned is very individual and each individual needs to be looked at as a whole with

the way they function for themselves, within society as a whole, as they develop as people, or sociable. And in this case you know our bottom line.

Now I am a high school science teacher, educator, and know about research because I teach research. I supervise the school's science fairs and set up the protocols for students and I am very hardnosed about things like controls and setting conditions under well controlled conditions. This is what I would like to address this morning: I have no complaint with some of the research design at least as I saw it and I became -- you know, was able to understand it in terms of the scientific product. It is very difficult to establish controls on a human being. It is not a tomato plant and it is not a guppy. This is a person who interacts with society in a particular way.

I will just be brief, okay, because I am getting signs that three minutes is too short to tell the whole story. What I would suggest in all the treatment at NIMH, which is right here, is that there be established, first of all, an ombudsman who can be objective and outside of the research in terms of listening to the patient so that this is definitely a part of the research design.

And there is something else there because there were times when just from needle sticks they were doing for procedures Andy developed phlebitis and the nurse who is very objective and does not interfere in research either said, "Well, he has a scratch on his arm," but he did not. This was a life-threatening problem and it took a doctor who knew how nurses react and how dispassionate they are to sit with him all day and just put ice on and avoid the terrible consequences of a phlebitis.

So, first of all -- you know, so this dispassionate attitude is one that needs attention, specially prepared nurses be there, an ombudsman be there, and that the people have a way of informing society around there that they are especially ill and under special treatment.

He was home one time visiting and he had an episode. I do not know whether it was panic or whatever. But my husband and I did not know what to do. We were afraid to call an ambulance unit because they would not want to do. They had no indication and they would possibly give him something that would counter, you know, counterindicate what medications he was on and whatnot. We had no recourse.

Well, why can't this people have beepers? Access to an emergency so that somebody knows what is happening to them. Somebody possibly who knows what to do. I mean this should be a relatively simple safeguard for those people who are in blinded studies.

Now I could go on and on but those are practical proposals for taking care of the blinded nature of these studies and confidentiality, and their vulnerability in terms of not being able to tell anybody what is happening, or believed because they are

psychiatric patients. People say, "Oh, they are crazy," and they do not listen.

DR. CHILDRESS: Thank you. We will look forward again to receiving the written report which will flush some of this out and also any further recommendations you might have.

Our last speaker for the morning is Dr. Vukov. Okay. Again five minutes only and we do have written testimony that has been circulated this morning to the commissions so you should have that in front of you.

DR. VUKOV: I am Dr. Judith Vukov from Los Angeles and I am going to speak to you about the abandonment and neglect of my daughter and the misrepresentation by the research team in regards to my daughter, Abby.

I am not only a grieving mother but I am also a practicing psychiatrist. My daughter, Abby, at age 25 died four years ago this month. She died of aspirin toxicity and undue delay in diagnosis according to the coroner at a local ER 15 miles away from the state hospital and the research unit.

Abby died because she was placed at risk as a research subject. Even when her condition became life threatening and she was neglected the research records reveal that there was no attempt to intervene either medically or psychiatrically.

Later an investigation by the California Health Department revealed: (1) that there were no nurses or doctors there for the last 18 days of Abby's life. (2) that the research team misrepresented unit 45 as an acute care unit when, in fact, it was only an immediate care facility also known as a group home. (3) Abby had been administered Tylenol 13 years by the nonprofessional staff during the last week of her life and there were no physician notes indicating why or what the reasoning was, or why nothing else was given. There was also no treatment plan for the 54 days that she was on the unit.

I might also add that on the night that Abby lay dying in the emergency room the night staff recorded her as alive and well on their unit.

Abby's case was pivotal in the L.A. County decision to bar all conservatees from participation in research of any kind in Los Angeles County or apparently in any other county in California.

Later from information received from a FOIA request it became apparent that the research team also adjusted her diagnosis to fit the protocol and ignored her medical history. If they had complied with the inclusion and exclusion requirements she would never have been in the research.

(1) to be included in the research one must have a clear cut diagnosis of schizophrenia. The UCLA team ignored their own findings of bipolar disorder with organic features and placed her in the research. They also ignored all the previous diagnoses by previous doctors, none of which was schizophrenia.

(2) the exclusion criteria said that there should be no

history of neurologic conditions. Abby had Tourette's Syndrome. She had Siddenham's Chorea. She had also had been the victim of two assaults in the previous month in the state hospital and had two head injuries.

When Abby's condition deteriorated and dramatically changed for the worse by documented by the very sparse records instead of reverting to standard practices they had promised in their informed consent the researchers only utilized --

(Technical difficulties.)

DR. CHILDRESS: I am very sorry.

DR. VUKOV: Can you hear me? Is it still on? Is it on?

DR. CHILDRESS: The recording is working.

DR. VUKOV: Okay. I was going to say that the researchers utilized behavior modification and shunning, a practice that was outlawed by the L.A. County Patient's Rights Division many years before and which I cannot use as a private psychiatrist.

The attitude of the UCLA team to my daughter's death and the findings of the investigations can be summed up in a statement by the head of the team in a fact finding event.

When asked if he kept records about Abby's death he said, "If I saved all the material that came across my desk I would not be able to sit down." Thus the findings about my daughter's death only filled his wastebasket.

I, too, once believed that research would turn Abby's life around. It turned my life around 40 years ago in a study with the endoscopy tube and I might say the researcher still knows me and still knows my name 40 years later.

I think that attitude in this country has changed and that care and consideration. From what I now know I use every new drug with trepidation knowing that was uncovered in the investigation of Abby's tragedy and that of others is systemic and pervades all levels of the research community.

To sum up my feelings and those of others the L.A. Patient's Rights said to me that if this had happened in a private hospital they would have pulled their license and shut them down. I was shocked.

The recommendations I would like to make is that there is an autonomous doctor outside of the research community, an internist. Apparently researchers do not believe that these people get physically ill from the psychiatric medications or whatever medications they are being administered. I do not think the psychiatrists or even the research psychiatrist today knows enough about internal medicine anymore to protect the patient or cares enough and I also do not think the nurses know enough. I think there needs to be an independent treatment team watching out for the welfare of the patients.

I also think that there should be sanctions for the violations of state and federal law. I think that once this happens anywhere in this country NIH should stop all funding of all research

going to that institution. I really resent the fact that these people are still being funded with million plus grants every year since Abby died.

You say -- somebody here mentioned to go to OPRR. I wrote to OPRR a year-and-a-half ago. I was just informed by them that the woman who was supposed to be investigating left her position so it still has not been investigated.

You also said to talk to your attorney general. The attorney general protects the employees of the state. They do not protect the patients. In our case the attorney general supplied the legal counsel for the doctors. You cannot go to the attorney general. The attorney generals are there for the state only and their employees, not the rest of us. We have to go to the federal government.

Thank you.

DR. CHILDRESS: Thank you. Could you remain just a moment and let me see if there are any comments?

Thank you very much for sharing this very moving story.

I thank everyone who has presented today including those who presented written testimony only. We are glad to have both when it can be made available.

These stories and in many cases the explicit recommendations that follow the stories and in other cases the implicit ones will be very important for us as we deliberate our report and our recommendations of possible guidelines and the like. So we are grateful to all of you who took off time to join us today and bring your stories before us.

We obviously are still running behind and we will need to assemble at 1:00 o'clock so you will have 47 minutes for lunch.

We will begin with the T.D. case. I talked to all the parties who are planning to discuss that and all of them can remain until the early part of the afternoon so we will do that as the first matter on our agenda this afternoon and then turn to our own deliberations.

I thank everyone again.

(Whereupon, a luncheon recess was taken at 12:14 p.m.)

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

DR. CHILDRESS: Thank you for rushing back from lunch. I am very grateful to you since we have a full afternoon.

We will have additional public testimony on the topic of decisionally impaired subjects at our next meeting. At least one other person at the end of the meeting today indicated they had decided to testify. Since it became so late and our schedule is so tight and he has submitted written testimony to us he agreed to testify in October. I am sure there will be others as well when we follow up.

Another part of what we had planned for the morning that we have to do in the afternoon is to discuss the T.D. case that you are familiar with having received the case before. The case that was hard to read.

We have with us parties who have been involved and remain involved with this particular case for the first part of this discussion and limited to ten minutes of presentation, however they choose to divide it among the participants, and you have their names on the sheet, are Stephan Haimowitz, who is assistant counsel in New York State Office of Mental Health; John Oldham, New York State Psychiatric Institute and so forth; and then joining in the question and answer period will be Susan Delano who is clinical research coordinator for the Research Foundation for Mental Hygiene.

And then after we have had our discussion with them we will turn to Ruth Lowenkron.

All right.

Again you are free to work out that ten minute slot however you wish.

DR. OLDHAM: Thank you very much.

I am John Oldham and Steve and I are going to be making some remarks and we will do our best to divide the time roughly between us.

I would like to just quickly say a word about the case from the point of view of the New York State Office of Mental Health. First of all, I appreciate the opportunity to talk to this commission and I think the task that you are engaged in is extremely important. We feel very strongly that it is critically important to support that when research is done it is done in an ethical way and it is done to maximize benefit and to minimize risk.

In fact, the T.D. case emerged as a result of a process that we began in the Office of Mental Health in an effort back in the late '80s to try and strengthen protection for research subjects. The agency, the Office of Mental Health, had earlier research regulations that we did not feel were sufficiently protective and after a lengthy public disclosure process we -- after public comment and interaction with many, many different groups, including advocacy groups, which also included the advocacy groups who later were the plaintiffs in the litigation, negotiated and ended up accepting new regulations in the Office of Mental Health,

which we thought provided greater protection to vulnerable populations.

One example of that was that when there were patients with questionable capacity to sign informed consent prior to the new regulations the director of an inpatient facility was allowed to be the surrogate consenting signer for such a participant in research. We did not feel that was appropriate and we changed that by the new regulations.

In 1991 litigation was filed, the T.D. case, and it was filed by three different advocacy legal groups on behalf of six patients who were hospitalized in state facilities. It is important to know that none of these six patients had ever participated in research to our knowledge. All six of them, however, had been given medication against their will through the standard New York legal procedure of court authorized administration of medication and it was contended that these six patients were fearful that they might be involuntarily required to participate in research.

It turned out that this case went before the trial court in New York and this went on for several years and eventually a decision was reached by the trial court. The case was brought in two major categories and Steve Haimowitz will tell you a little bit more about that.

One jurisdictional which indicated that the contention of the plaintiffs was that the Office of Mental Health did not have jurisdiction to issue regulations but only the Department of Health. The second part of the case was more substantive with contentions on the part of the plaintiffs that there was a highly risky research being done that was quite harmful to patients who were vulnerable and they made a whole series of allegations in their papers about the content and substance of research.

We appealed this case after it had been found in the trial court to be in favor of the plaintiffs. The response from the defense was to focus specifically on jurisdictional and constitutional questions and not to respond with regard to the substantive issues and unfortunately that strategy became a problem because the court record that was laid down included a series of unsubstantiated allegations on the part of the plaintiffs with no exploration of those issues.

I would just mention a couple of examples of that and specify a couple of problems that we are quite concerned about. One is that, in fact, the plaintiffs contend that there is highly risky research being done in the Office of Mental Health operated or licensed facilities and that it is being done with patients who are being asked to participate in research but that it is nonconsentual as the plaintiffs' claim and they also contend that not only is this highly risky but that it does not offer -- and I am quoting here -- "one iota of benefit."

One of the problems is that we do not agree that many of these contentions are true. As far as we can tell and to our

knowledge there is no research that the Office of Mental Health licensed or operated facilities is doing that is high risk in our opinion. In many efforts to settle this case in discussions with the plaintiffs' attorneys we attempted to agree upon the concept that is in the federal regulations for children which is the notion of a minor increase over minimal risk. To our knowledge there is no research being done in New York other than at a risk level that we would categorize as a minor increase over minimal risk.

A second critical point is that the plaintiffs have required and the court has accepted that all protocols be defined as nontherapeutic in their entirety if any element of the protocol is nontherapeutic. Therefore, any single component of a research protocol that is nontherapeutic will categorize the entire protocol as nontherapeutic. The result of that, we think, is enormously unfortunate.

Let me just mention one example of how this becomes a real problem in just a moment. Let me just add that once this decision was made by the appellate decision after we had appealed the case it was upheld by the appellate division in New York. This is the First Appellate Department, which is Manhattan and the Bronx. At that point the decision of that court was to limit the scope of the finding in favor of the plaintiffs but only for nonfederally funded studies.

The plaintiffs have at this point petitioned and made a motion to the state's highest court, the Court of Appeals, requesting that the findings of the Appellate Division be extended to apply to federally funded studies as well and also to therapeutic studies. That is now on the Court of Appeals' calendar.

The example of the problem that is created by this is illustrated by the following example: We have a federally funded research protocol at my institute which involves adolescent suicidal patients. Adolescent suicide -- suicide is the third leading cause of death of adolescents. Suicide in this age group has increased over 200 percent in the last ten years.

This protocol involves hospital based treatment for up to three months, at no cost to the patient, which is extremely therapeutic. One component of this study is a lumbar puncture which is required in order to get central nervous system serotonin levels, which is a critical component of the study to determine if by this means we can identify those at highest risk to enable us to have a prevention strategy for this extremely devastating condition.

This is in our view a highly therapeutic protocol but because it contains a lumbar puncture it is now defined as entirely nontherapeutic. At the present time it is only possible to continue to do this because it is federally funded. If the Court of Appeals were to decide in favor of the plaintiffs this would now be illegal in this state.

Our concern is although it is limited at this point to psychiatric patients that the principles apply to subjects under the

age of 18 and all adults where there is a question of capacity to consent. That could well establish principles that could go well beyond psychiatric patients to other medical conditions as well.

Steve?

MR. HAIMOWITZ: Thank you. I want to make two very brief points. One on the point that Dr. Oldham just made about the classification of protocols.

As a result of the court decision it is now the case in New York that a protocol which is predominantly therapeutic, if it has a single nontherapeutic element the entire protocol is considered nontherapeutic, and if it is not federally funded it is prohibited. Think of it in terms of what we have learned in the last decade about at least for the HIV/AIDS community the desire to look at research as a means of access to getting, hopefully, effective treatments out there more quickly than would otherwise occur or in the area of the struggle that goes on with HMO's to get cancer treatments that are still experimental paid for by patients.

As a result of the decision the access to, hopefully, helpful medications are limited for people that are incapable and the science that could be generated by their participation in therapeutic research is also impeded. The other thing that is interesting to note is that if you contrast the situation in New York with both the federal regulations and in the effort underway in Maryland to think about these issues in a coherent way you have New York taking the position by its court's ruling on the constitutional questions that the traditional notion that an IRB looks at the entire protocol and assesses the reasonability of the risks in relation to the benefits, that no longer is legal in New York if there is a single nontherapeutic element that precludes at least some people's participation in the research.

The one other point that I wanted to make quickly is that people often ask us how could this occur. How could what looks like an outcome which is at least in part problematic, how could it be the constitutional law of New York? The answer is that for reasons having to do with legal strategy, the attorneys handling the case at the time, decided to present this case as one of what is called motions -- request motions for summary judgment. That is the issue was framed in terms of constitutional principles that had evolved in other areas of health care.

As a result the characterization repeatedly made about the kind of research that is involved here of it being life-threatening, high risk, no benefit was a characterization that the court having heard it so many times ultimately accepted as true without there being any examination in the court of the question of how you look at risks of research participation as contrasted with standard treatment as contrasted with the illness itself.

How do you assess benefits? The entire question was something that, though identified in some court papers, was never examined by the court. As a result of the decision at least in New

York when the court decides a matter as a question of constitutional of law, to a large degree it ends the dialogue. It ends the debate. Our concern is that whether it is psychiatric research or pediatric research, or neurological research, that this sort of paradigm presented by the New York courts or announced by the New York courts will begin to be viewed around the country as the paradigm to be applied.

We hope that, of course, this commission will look at the reality of research and come up with more workable -- principled and more workable concepts that will guide research.

If there are any questions I am sure John and I would be happy to try to answer them.

DR. CHILDRESS: Well, thank you both and thank you for packing it all into the time limit too. That is very impressive.

If all three of you -- if you would like to -- well, be where you can reach the microphone.

Alex Capron has a question first.

MR. CAPRON: I would like your help in unpacking these categories of mixed therapy and research. There are certainly situations in which a standard form of therapy is being given and added to that would be a new therapeutic agent. A second category would be a standard therapy is being given and the desire now is to do a research procedure of the type that you mentioned of taking the spinal fluid because a question has never been answered what is the diagnostic sign that might say that although it is effective with all these people, maybe some need it more than others or it is going to be more effective in one group or another, make some differentiation without changing the therapy.

Then there would be situations in which you are trying out a new agent which you hope and believe would be therapeutic based upon the preclinical use and along with that would be monitoring the outcomes and doing some tests of the type that you describe.

Now in all of those one could say this is "therapeutic research." One of our predecessor commissions and one of its staff members, Robert Levine, has been lobbying for 20 some years to get us all to drop the term "therapeutic research" because of its potential to confuse both the investigator and the subject. I just stick with the terminology because you have used it.

Wouldn't you say that there are substantial differences in these three, and if you would like any additional types, of mixed therapy and research?

DR. OLDHAM: Yes. I would just say a word about that. It is obviously a very complex area and I am familiar with Robert Levine's argument and pretty much agree with it.

The problem is that the whole notion of how you sort of -- the principle we have followed has been that our charge to the IRBs has been that their job is to assess risk and benefit and to adjudge the overall benefit and assume that it outweighs any

significant risk.

Overall the problem is that as we understand this court proceeding, and as the court seems to have accepted the definitions, any process that is involved as a component of a research study, even if in fact it is a comparison of two already established therapeutic agents, but you are studying something to determine whether there is a difference between one group and another, and that is not a test that would ordinarily be done in the routine part of treatment with those medications or treatments, that that is the nontherapeutic element that would then categorize the entire study as nontherapeutic.

Likewise if there is something like a PET scan that needs to be done as a component, let's say, of a new medication that is in Phase III or Phase IV trials, that would no longer be possible either. Now we are only talking about research with the populations in question but it is all subjects under the age of 18 and, in fact, adults where there is a question of capacity.

But the definition as the courts have construed as we understand it is categorical and inflexible in that way.

In contrast, I might say, to the plan that we think is very reasonable being put together by the attorney general's office in Maryland providing a work group product that recommends an overall assessment of benefit and designating protocols as therapeutic or beneficial if overall they are beneficial even if they contain some element that is nontherapeutic.

MR. CAPRON: What I wondered is you gave a particular example of people who -- teenagers -- who would definitely fall within the category where this question is going to arise and for whom the intervention that you are talking about is very important because otherwise behavioral manifestations are disastrous. Is that correct?

DR. OLDHAM: That is correct.

MR. CAPRON: Now if that were the case then if you were decoupling the -- that intervention from the spinal tap then there would be nothing that would prevent you from doing -- from providing the treatment, right?

DR. OLDHAM: That is correct.

MR. CAPRON: Is this an established treatment? Are you in the category then?

DR. OLDHAM: Absolutely.

MR. CAPRON: So you are doing the spinal tap.

DR. OLDHAM: The reason that is, I hope, a pertinent example is because, in fact, it has been determined in adults that low central nervous system serotonin levels are predictive of the very highest risk category for research -- I mean for suicides. Sorry. Suicidal risk.

It has already also clearly been established by many, many publications that you cannot automatically assume that what has been found to be true in adults applies to children and adolescents

and yet in adolescents the suicide rate is among the highest there is. This particular finding happens to be critical as part of this research protocol and is exactly what would not be allowed.

MR. CAPRON: Just so I can understand further, it would be -- would it or would it not be the case that these patients would otherwise be given this treatment? This is now the standard treatment. You are just testing this diagnostic marker?

DR. OLDHAM: In this particular case at this particular institute this treatment is probably more extensive, more intensive and more available than would otherwise be available but it would not otherwise be available at the institute which is funded by the state to do research. These people have this entire treatment in the context of the research protocol and it is at no cost to them. They would otherwise need to apply for whatever third party covered treatment or public support treatment that could be available elsewhere.

MR. CAPRON: So if hospitalized in another hospital they would not get this treatment?

DR. OLDHAM: They would get whatever that hospital offered in terms of treatment. I do not think, frankly, in the era of managed care these days that it would be likely they would come close to the kind of treatment that this protocol provides but that is one specific example.

MR. CAPRON: I mean all of this begins to have some of the sound of the Willowbrook experience and I do not mean to paint with too broad a brush but the parents there were also being told that the -- in that case the condition was hepatitis was endemic in the institution, that they needed this institution because there was nothing else to do for their children by way of treatment.

If they wanted to get into the institution the only way -- the only door that was open in an over crowded institution was the door to the research unit and they would have to then agree to allowing their child to be given hepatitis and afterwards people, David Rothman and others, writing about this made clear that the parents here really felt they had no choice.

What you are describing is people who need the treatment, the only really effective treatment is the one you are describing, and the only place they can get it is at a research institution.

DR. OLDHAM: Let me clarify --

MR. CAPRON: Is that a fair --

DR. OLDHAM: No, it is not. Let me clarify. I do not mean to -- I am not trying to make the point that this research institution is the place and the only place that this treatment can be provided. These teenagers who have suicidal depression should be able to get satisfactory adequate treatment lots of places. We are a very small facility. We have only 36 research beds and this protocol is only a small part of those. So there are not many numbers we are talking about here. We are not saying this is where

you need to come and then we are going to do research on you.

What we are saying is, in fact, that if, in fact, you evaluate this entire protocol, one component of which is crucial for this study, by the way we think it is very substantial benefit that is made available to these subjects who voluntary agree to participate and whose parents consent to this treatment. I would like to make that one clarifying point also which is that we -- unlike the contention by the plaintiffs that this is nonconsentual research -- do not do research with patients if they do not assent to the treatment, both children and adults, regardless of capacity.

MR. CAPRON: If I may just ask one final question.

In this particular case is the only place treatment like this is given is institutional or do people progress from institutional settings into outpatient settings?

DR. OLDHAM: They would progress but these are patients who are so suicidal that at this point in their illness the hospital based treatment is appropriate.

MR. CAPRON: The examination that you propose to do could only be done at that point in their illness?

DR. OLDHAM: As part of --

MR. CAPRON: Is it before they get the medication that you have to do it?

What I am wondering is obviously if the major concern here is this difficult question of the freedom of people to make choices and the ability of their families to protect them once they are in institutions and whether or not what we heard this morning is representative or not, it is certainly indicative that some people have found themselves in circumstances where they as individuals and the family members were unable to act in the normal protective way towards these institutionalized family members.

DR. OLDHAM: I understand your --

MR. CAPRON: So the reason I suppose the court, as I read the decision, is particularly concerned about it is that setting. If you were able in other words to -- not just you -- but anyone was able to give this treatment. The patients then are returned to a home setting where they are taking the treatment and then a sample of them agree, and some will not agree but some would agree, to have their spinal fluid examined to see whether the pattern of variation is the same in them as it is in adults. Then you would take yourself entirely out of this.

You would still get the research results you need and you would not have the sense that people who were desperate to get into an institution because their managed care plan or their hospital does not provide the appropriate treatment are saying to you, "Well, if I have to do this," or they are saying to you, "I hear you talking about therapy and I do not really hear you talking about research," is what we heard from a lot of people, "so I will sign the forms. I will come in and I will read all of this." That is what is so worrisome in all this.

DR. OLDHAM: Well, first of all, I understand the concern. I know the situation about the Willowbrook situation and these are very, very real and serious concerns. I would add, though, it is my contention that there is light years of difference between what goes on in very carefully presented and much more, I hope, and I think I am correct on this, dialogue that is timely and careful and informative in the process so that I was disturbed just as you were, I am sure, to hear some of these testimonies earlier today.

However, let me make one other point in response to your particular point. I think I am correct -- and, Steve, correct me if I misunderstand -- but it would not matter in this particular case because these subjects are under the age of 18 and that is all that determines the decision. So it does not matter whether they are in the institution or not.

MR. CAPRON: I thought the regulations applied to research done at these state run and state licensed facilities. Is there any private physician in the State of New York?

DR. OLDHAM: The regulations apply to the Office of Mental Health operated and licensed facilities and do not specify inpatient or outpatient. Therefore, any clinic, any outpatient clinic that bills Medicaid or Medicare is covered by this suit.

DR. CHILDRESS: Alta?

MS. CHARO: No, Alex actually covered very close to what I was going to ask so I will pass to Arturo.

DR. BRITO: A specific question about -- I understand your point about the component that can determine the entire research protocol illegal in your state now. My question is who determines or what is determining that that component, we are talking about the spinal tap specifically here, that that is more than minimal risk because if you look at numbers it truly is not more than minimal risk. So are you implying that it has been determined that that is more than minimal risk because of the small possibility?

DR. OLDHAM: Well, in our view -- we have actually tried to research this question because this particular procedure, a lumbar puncture, is one that has come up. Others that have come up have been PET studies, PET scans, which are also what in this litigation are used as examples of more than minimal risk and are sort of globally swept into what the plaintiffs refer to as highly lethal/highly risky procedures.

This particular lumbar puncture in our research of the literature, although it can be occasionally something that produces discomfort, is done widely. It is done every day in every general hospital. It is done with local anesthesia and is usually not painful in routine cases and about ten percent of the time can produce a bad headache that usually resolves within 24 hours.

My own view, most of us in the institute would characterize this, in fact, as minimal risk. There are those who

would agree and it has been proposed that it would be certainly no more than a minor increase over minimal risk and we would be comfortable with that. That has been a category that the plaintiffs in this case have not been willing to accept and at least as they have defined things in the context of the litigation these have been procedures that they have insisted on categorizing as high risk.

DR. CHILDRESS: Any other questions or comments from the commissioners?

Bernie?

DR. LO: Can I ask a question -- I would ask you to answer it from your hat as someone who is directing a large research program at an institution as opposed to one of the parties involved in this case.

This morning we heard a lot of testimony expressing concerns that family members were not part of the decision making process either at the onset of the research or the continuing phase of the research, that there may not have been opportunity to withdraw from the study after once enrolling, particularly in the context of sort of a closed institution as opposed to an outpatient.

Do you think your regulations in New York address those issues? If not, how would you suggest responding to the concerns we heard this morning?

DR. OLDHAM: Let me just say a word about this and I might ask Susan Delano, whose responsibilities include oversight of the IRB for all of the state operated and licensed facilities. I hope that I am correct, and I think I am, that we do a hard job to try to be very careful and conscientious and attentive to these kinds of concerns. We charge our IRB to be very, very conscientious and careful and scrupulous in its review.

We, in fact, make it very clear to our investigators that they need to proceed with using informed consent not as a one signature concept but as an ongoing process that goes throughout the course of the person's hospitalization and we make it very clear to all participants in research that it is their right at any time to withdraw, to object to continued participation, and the moment they do so we withdraw them from the study. We encourage our researchers to repeatedly make that clear.

We also have a research monitor who is constantly reviewing the records of our research protocols and bringing any concerns and questions to our attention that we may not otherwise have known.

In addition, we have appointed specifically a patient consumer who is a former participant as a patient in research as a member of our IRB and we also have a family member of our IRB so that we have some of these pieces in place that we heard some talk of this morning and we think that those are useful suggestions.

Susan, would you add to that?

MS. DELANO: Yes. In the process of developing the regulations we were very concerned about the ability of patients to

object and we specifically wrote into the regulations a provision that not only should the objection of an incapable patient be honored but that any member of any of the classes of authorized surrogates could object and withdraw a patient from the study.

So, for instance, if a spouse had provided consent to participation in research and an adult child objected to that person's participation, that adult child would be authorized to withdraw the person from the research.

The only exception to these that was built in was that the objection of either the patient -- the objection of the patient could be overridden if a court application was made and the patient was found to be incapable and the court authorized treatment over objection within the context of the research. That provision for overriding the objection of a patient was put in for the specific purpose of allowing access to medications that were investigational where the only means of accessing a therapy was through a research protocol. To our knowledge that provision was never used. We anticipated that it would be an extremely rare event. So we were very conscious of that.

You raised a point, too, about the involvement of family members. When we were developing the classes of authorized surrogates we did in the regulations rely on family members to be the second line of surrogates to authorize. The first line of surrogates being surrogates chosen by the patient.

We also worked very hard in our research protocols to encourage patients to involve their family members to assist them in making decisions about research participation and where the family members agree we do provide information to family members about participation.

DR. CHILDRESS: We thank you very much for participating today in this discussion.

Now we turn to Ruth Lowenkron who represents Agency Disability Law Center and the New York Lawyers for Public Interest.

Ten minutes and then we will have a discussion.

MS. LOWENKRON: I am sorry.

DR. CHILDRESS: Ten minutes for your presentation and then discussion.

MS. LOWENKRON: Great. Thank you for inviting me here and I, too, like most of the speakers, would like to thank the commission for the work that it is doing and the fact that it is looking into these very important issues.

As Professor Childress mentioned I am with the Disability Law Center and New York Lawyers for the Public Interest and we are both one of the plaintiffs and one of the counsel in the T.D. case that the previous speakers have discussed. I will respond to a few things that they said but primarily stick to what I had prepared to tell you which is my recommendations for the committee that I come to after seven years of litigating this case and come to in part on the basis of what the T.D. decision holds.

I guess the most important thing I wanted to say in response is that the three individuals who spoke before will give you a complete different sense of what went before the court for the last seven years than what in reality happened. I think the best way for you all to know what happened is to take a look at the 3,000 pages worth of record, all of which were put together based on entirely -- based solely on documents that we received from the state. We are not making up stories. We are not here to have a fun time. We are not here to point fingers. We put into the record those experiments that were happening and they are there for anybody to see and we can discuss further.

I think what is also important to know is that the challenge was not only to what was actually going on, the experiments that were going on, which are noted in the record, but also the potentialities of the regulations, what the regulations would allow. I mean, in one way I suppose I should feel good that -- it seems that Dr. Oldham is boiling down the one problem to the kids with the -- where research cannot go forward because of the PET scan.

And, in fact, that is the posture they are taking in the litigation because they have not appealed this matter. We have appealed it as Dr. Oldham told you. The plaintiffs have appealed the matter to our highest court on the very narrow issue that the decision for an inexplicable reason decided to exempt federally funded research but the state is not appealing it.

The response that I would like to give with respect to the example that Dr. Oldham used is twofold. One is pointing to what Professor Capron was dealing with, which is there are a number of different projects that were not addressed in Dr. Oldham's testimony. In other words, those protocols where you are talking about an element that is nontherapeutic and part of an experiment which is not the normative treatment. So that is a whole different ball game and it has not been talked about.

But to stick with that very narrow area that Dr. Oldham talked about one of the things that can be done is an unbundling, to again pick up on the words of Professor Capron, and in fact when the court ordered a stop those kind of nontherapeutic treatments that is precisely what the Department of Mental Health did. They unbundled the experiments and so the individuals continued to get what was the normative treatment without in that instance -- I believe it was the spinal tap.

Okay. I assume you will have questions of me but I will get right into what I wanted to recommend. Again I think that a lot of it is based in the T.D. decision. I have provided you all with a copy of the decision as well as our Court of Appeals brief. I think what is critical is that formally the State of New York allowed -- and I should say to make very clear that the challenge and, therefore, my comments today, dealt solely with (a) greater than minimal risk research and (b) research on incapacitated adults and

children. So it is limiting a whole bunch of research that I am not going to be talking about. Needless to say some of the issues that were brought up before when you have someone who does have capacity and you run into problems and want to do minimal risk research.

In the context of that greater than minimal risk research on incapacitated adults and children what the state had been allowing was nontherapeutic research to be done on the basis of a surrogate -- for incapacitated adults on the basis of a surrogate's say so without any kind of a say so from the individual.

Yes, if the individual objected they would not do it and, of course, we think that is an important safeguard. But shy of an objection it was enough for a family member to say yes or no. The court found that that was impermissible. The court found based on due process rights that individuals have not to be experimented on and based on common law privacy rights that was impermissible and we strongly suggest that that is a line that should be taken in whatever it is that this committee comes out with. I should add that we would endorse that the committee comes out with regulations and not just guidelines. That you really have something more to sink your teeth into to have regulations.

So that is one aspect that we clearly endorse and also with respect to children the court found that when you are talking about nontherapeutic research that that cannot be performed on research, that a parent cannot consent to that kind of research on children. Again pointing to our common law -- our notions of privacy and our due process constitutional rights. I should add, too, that the courts, though they are New York State courts, they did not rely solely when you were talking about constitutional provisions, they did not rely solely on the state constitution but looked to the federal constitution as well.

With respect to possibly therapeutic and possibly beneficial experiments we did not say you cannot do them by any means. I am sorry, I should add that we are not putting a blanket, no, you cannot do nontherapeutic research on incapacitated adults. We are saying that where the incapacitated adult, when the incapacitated adult had capacity drafted a form of an advance directive, be that a proxy to make determinations or be that a written living will sort of a document. When such an animal exists that specifically delineates the individual's desire to be a part of nontherapeutic research that that is permissible as well.

I think the documents that have been distributed here by both Dr. Moreno and Professor Dresser talk about the abundance of literature going into advance directive issues. We endorse that as well as the protections that are in both of those articles as well in terms of ensuring that the individual has capacity when the directive is established.

I should also note in the documents that I provided to you part of the court papers have a research directive albeit for

the therapeutic context but that is also something that could be utilized by this committee.

Moving on to the context of possible therapeutic research there we are very clear in saying there too where there is an advance directive therapeutic research can go forward but it cannot go forward in the manner that the state had formerly said it could which is just again by the mere say so of a family member or a close friend.

I am already being told it is time.

Okay. I would just like to say that that is working really well in New York. There -- since the court stopped that kind of research there were a number of petitions made by hospitals to continue to do that possibly therapeutic research and in one instance it was uncovered that it was not possibly therapeutic, that it was nontherapeutic, and in four other instances it was just stopped. So I think it is a good mechanism. It is working.

In New York we have already a system in place where the courts are very accessible to patients in psychiatric facilities and it fits into that system well and the court is easily accessed.

The court in T.D. also gets into a number of issues with respect to notice about capacity and we would strongly endorse that those be followed. I guess I am going to do this real shorthand.

What we would like to suggest is that regulations come from this committee that address all human subjects research that are not limited just to those which involve federally funded research and that in addition regulations come out that empower OPRR or such an agency to actually do investigation of incidents so that all of the people who came here today could have felt that their incidents were investigated right then and there and not several years later when one complaint is filed, and that they have the ability to remedy abuses.

One thing that I think is real important, and this is something that I think Dr. Oldham and I agree on, that there are issues about what is minimal risk and what is greater than minimal risk. Certainly if you are going to throw into the mix this minor increase over minimal risk we would strongly endorse the concept put forth in the Dresser article that examples be given of what is clearly minimal risk and what is clearly greater than minimal risk so that there is often some uniformity.

With respect to minor increment over minimal risk we would caution against that and we feel it is a slippery slope and if you go that line that it be studied in depth to see how it works out and that it is narrowly defined.

The last one sentence is that we urge that the provisions in the regulations that talk about deferring to state law is important. We have seen it to be important now where New York has put so many protections in place for patients.

DR. CHILDRESS: Thank you.

Eric?

DR. CASSELL: After listening to both I am looking forward to what is the solution to be. Good persons on both sides who wear only white gloves, it cannot be the case. You can over protect just as you can damage research subjects. After all we have heard egregious examples of very bad things being done to people today. On the other hand Broadway in New York is the new mental institution because of the protection of the institutionalized subject and deinstitutionalization was done to protect patients against the bad things that happened in institutions so now they sit on Broadway instead.

So the problem with this is -- you do not know what I mean?

MS. LOWENKRON: No, I -- I guess I would differ from you as to why they are sitting on Broadway.

DR. CASSELL: Of course you would differ. That is exactly the point.

MS. LOWENKRON: Yes.

DR. CASSELL: The point is that if we listen just to this or just to that it is very hard to know how to protect subjects on the one hand and make sure on the other hand that things that are important get done. That is the problem. The problem is not putting a wall to stop what one group thinks is bad or to keep going when another group thinks it is good. The problem is how, in fact, to protect subjects who do not have full capacity at the same time as the illnesses which make them not have full capacity get adequately treated and adequate research done?

I must say listening to this rubric I have not heard it in these two sets of testimonies. I have not heard that protection. I have not heard it from you and I have not heard it from them.

DR. CHILDRESS: Would you like to respond?

MS. LOWENKRON: I am not sure I know how to respond to that other than obviously I think that we are seriously looking at protecting the rights of patients but we are not here advocating that no research go forward. We recognize the benefits of research. I think we attempt to counter the concept that putting these protections in place will send research hurtling back into the dark ages.

DR. CASSELL: Don't over do it. If that is what makes it difficult -- when you over do it then it makes it very hard to know exactly what you mean. It is like when you say a slight increment over minimal risk, that is a slippery slope. There is no question about it. What are the protections to be on the slippery slope?

MS. LOWENKRON: I appreciate what you are saying. I think I was not really engaging in hyperbole that was not out there. There was not the sense thrown -- within the context of this litigation that putting the protections in place that we were suggesting would stop research. It was specifically suggested in the context of AIDS dementia and Alzheimer's dementia that no

research could go forward.

I think that one of the important things to think about that I think is sort of a middle ground and is responsive to what you are saying is taking a look at these advance directives, that is how research is going to go forward for the population of people who are incapacitated where we are saying they cannot be put in research by somebody else. They can only be put there if they, themselves, say so but how are you going to get them to say it if they are incapacitated. Well, I think that the dilemma is answered in large part by the concept of these advance directives assuming that appropriate safeguards are in place.

MR. CAPRON: But not for children?

MS. LOWENKRON: But not for children.

DR. CHILDRESS: Bernie?

DR. LO: I wanted to ask two questions. First I agree that it would be nice to try and give some substance to concepts like minimal risk. The previous speaker suggested that PET scans and lumbar punctures are certainly no worse than a slight increment over minimal risk and may even be minimal risk.

I ask you to comment whether you think in the context if someone who is depressed or psychotic those procedures are minimal risk?

My second question is to advance directives. How feasible do you think they are in the sense that advance directives for treatment decisions as opposed to research decisions are not very widely used and no one seems to think that there are reasons to suspect that people will fill out advance directives for research any more than they will fill them out for their own treatment.

So if we make that the sort of sine qua non of consenting to allow these certain types of research are we not, in essence, saying that research probably will not happen because so few people will complete the advance directive and that you just will not have the subject pool to draw upon?

MS. LOWENKRON: Well, I mean a couple of responses -- well, I will pick up on the second first. One is that because it is hard to get people to sign on to them is not enough for me to feel like that we should not do that. I think this again goes into that category of responding to -- you know, putting more protections in place is not going to stop research.

I think you also want to look at why is it that people perhaps are not going to be signing research directives with respect to nontherapeutic research. If it is because "people in their right minds" would not want to be involved in research which offers only risk and no benefit in the context of nontherapeutic research then I think that is something that we have got to be looking at.

DR. LO: That may be one reason that all the evidence with advanced directives in the therapeutic context is the contrary. When people say, yes, they are interested; yes, they would like to fill them out, they never fill them out. So, you know, the legal

formality with the form which are required in states like New York, in fact, may be the deterrent.

MS. LOWENKRON: Yes. I mean I think there is a bit of a difference between the person on the street who does not bother to sign an advance directive or sign the back of their license, you know, with the best intentions wanting to give -- you know, donate organs and someone just does not get to it, does not do it, what have you.

And the people that we are talking about in this context are -- these are people who are intimately involved with the system who are having treatment and who are in and out of hospitals, especially when you are talking about cyclical disabilities, there is certainly an ability to talk to people on the up side, on the capacitated side of the cycle. And I am not for saying it cannot be done without an effort to do it and I think the literature is out there. NIH for one is engaged in -- is utilizing these directives. My sense is it is do-able.

DR. LO: Thank you.

DR. CHILDRESS: I have Zeke and then Alex.

DR. EMANUEL: My questions are similar to Bernie's.

That the NIH is doing it and that is do-able are two different things. I think all the evidence that we know about in the literature of advance directives suggests that they are not workable and all of your suggestions are just beliefs and not data driven. I mean the data is that the barriers are enormous and unlikely to be overcome even for people who face imminent death. If you look at the cancer population who are dying and look at advance directive fulfillment it is small. Less than 50 percent. So there is no reason to believe the assertion you just made, it seems to me, that we are likely to get it and just because it is difficult we should not do it.

If your view is this is the only way you can have research going on it seems to me you have created an unscalable barrier unless you can produce data in any trial that there is reasons to believe you are going to get a reasonable number of people to do them.

The second thing is I would like you to answer Bernie's first question, which is from what I know or expect PET scans for one probably are reasonably thought to be -- or should be reasonably thought to be minor minimal risk items, small increment over minimal risk. Lumbar punctures the same I would think.

What is your evaluation of that?

MS. LOWENKRON: I think it is difficult to say because obviously there is literature about the risk of these kinds of procedures as well. It is very hard to suggest that this is minimal risk. But I turn it back to you to say you, not necessarily the ethicists amongst you, but you, the physicians amongst you, the researchers amongst you, it is exactly the kind of guidance that we should have. What is minimal risk and what is not minimal risk?

So my sense is that it is greater than minimal risk but I think this is precisely where work needs to be done.

DR. EMANUEL: Minimal is not zero risk. No one defines minimal risk as zero risk. So the question I actually would ask, rather than turn it back to us, since risk is not something necessarily that there is expertise on, right, part of the issue of minimal risk is that it is a perceptual question, what qualifies in your book as minimal risk?

MS. LOWENKRON: What qualifies as minimal risk?

DR. EMANUEL: Yes.

MS. LOWENKRON: I can give you some of my list. I mean some of the things like certainly observations are minimal risk. Things like taking a minor amount of blood is minimal risk. Things like giving aspirin are minimal risk. There are things that are very obviously minimal risk.

I think that already when you are moving on to spinal taps that you are talking about something that is elevated and where there are going to be people who disagree. My feeling is that is greater than minimal risk. I am suggesting that is precisely the guidance that is needed. It is not so important what do I feel about it I think as the suggestion that there should be some attempts for uniformity that this committee could be helpful with.

DR. CHILDRESS: I have two more questions listed. Alex and then Arturo.

MR. CAPRON: I am laboring with not just the effects of a cold but what a cold does to your brain so I probably know the answer to this but I just need you to tell me. Is the effect in the order in New York, is it your position that research which is intended to be therapeutic, that is to say it is a trial of a new treatment for an otherwise ineffectually treated disease, is that included as something which is not possible because of the -- in incapacitated adults or in a child under this order?

MS. LOWENKRON: No. I probably breezed through that too quickly. I mean we have divided the universe into nontherapeutic and possibly therapeutic and possibly therapeutic goes forward for the incapacitated adult if either he or she has some sort of a directive or if the court suggests that this states that the treatment is appropriate doing an analysis of what other available treatments there are and looking at the risks and benefits and so on.

With respect to children the parents have the ability to say yea or nay to that if it were a treatment modality.

MR. CAPRON: I mean it is my sense that actually there is a larger scope of risk and harm that arises in research which is denominated therapeutic than there probably is in the addition of minor monitoring and assessment research techniques on to standard therapies.

So, I mean, I think there is -- it is a problem not necessarily for you or your court order but there is a problem for

us in dealing with this. Probably more harm has been done in the -- and recently with the encouragement of the subjects involved particularly in the AIDS community -- of enrolling people into research which had bad effects on them.

Sometimes the bad effect of keeping them away from something that was more effective but more often just because the enthusiasm of the investigators and their willingness to say this is therapeutic, i.e. I would not be doing this if I did not hope it would help someone, but it turns out it does not, it has bad effects for them, is a much greater -- would fill more shelves with those studies than the people who have been harmed by having other techniques of assessment and, therefore, being treated as research subjects correctly described are in a research protocol. It is designed to answer an answerable question of generalizable knowledge as opposed to those same interventions being used without that assessment.

So it really -- I am with Eric in saying I regard everybody who is talking right now as all wanting to do the right thing and it just -- I think it is very, very hard for us to generalize about what that right thing is.

MS. LOWENKRON: Just to respond real briefly without getting into where there is greater harm, I think what is important or what we saw as important and I think what the court saw as important is that with respect to the possibly therapeutic there is also great risk and that is why there are great protections that are put in for that population as well. I think that is an important part of my recommendations to you that not just anybody can put someone into that kind of research and that it has to be heavily weighed and balanced.

MR. CAPRON: Will you be supplying a listing of those recommendations to us after the fact? Since there are obviously some you did not get to say given the limit of time.

MS. LOWENKRON: What I can do is refer you to the court brief where we put all this stuff in. It is about 50 --

DR. CHILDRESS: It came to my office yesterday. NBAC did not get one so it has not been copied.

MS. LOWENKRON: Oh, I see. But the recommendations are in there and the relief that we are requesting.

DR. CHILDRESS: So we will get copies made.

MS. LOWENKRON: Yes.

DR. CASSELL: Well, I want to make a plea. It is a thick document and I cannot believe that the recommendations occupy that whole document. So if you could have somebody just summarize the recommendations so that they really get read and they really get appreciated that would be of great help.

MS. LOWENKRON: Sure, I would be glad to do that.

DR. CHILDRESS: Thanks, Eric.

Arturo?

DR. BRITO: I just have a comment and then a question

about clarification on something you said. The issue with the lumbar puncture as minimal risk. As a pediatrician and as a clinician I do not see it as much more than minimal risk in the right hands and if it is explained appropriately to parents of children or the adult themselves.

In a book we received earlier on ethical issues and with mental health issues and children and adolescents from Fisher and Holgood (?) they do a really nice description of what minimal risk or things above minimal risk are, including psychological risks of doing tests. And they have shown or they refer to studies that have shown venopunctures and spinal taps are not anything more than minimal risk. I just want to clarify that.

In reference to something you said about -- did you make a suggestion that in children -- I know we are going to get to children later but I think this can also apply to cognitively impaired adults -- that when research involves nontherapeutic benefits or what appears to be nontherapeutic at the time that the research is being done, were you suggesting that absolutely that should not be done? We should make recommendations not to allow that?

MS. LOWENKRON: With respect to children?

DR. BRITO: Yes.

MS. LOWENKRON: Are we sticking with children?

DR. BRITO: Yes.

MS. LOWENKRON: Yes, and our recommendation will be that that be unbundled from treatment.

DR. BRITO: Okay. What I have to say about that is that I think sometimes what appears to be nontherapeutic at the time becomes therapeutic later and if it presents only minimal or just slightly above minimal risk, which is yet to be determined and maybe everybody will come up with some guidelines that actually determines that, but I think it also can be unethical not to do research sometimes.

So let's not swing the pendulum to the other extreme where we stop doing research because it can also be unethical in situations where there are therapies that are known to be effective in certain mental disorders in children or adults and that where nontherapeutic research can actually help understand the disease and later on provide some therapies.

So we have to be very careful to do that. I think sometimes you have to do nontherapeutic research to later on find out what the correct therapy is.

MS. LOWENKRON: Obviously it all boils down to whether you are talking -- in your discussion of ethics whether you are talking about what you owe to the people who present the symptoms or what you owe to the individual who is in front of you. I personally do not see a position where when you have a person in front of you who is not going to benefit where you have not any kind of ethical obligation to do any research. It is nontherapeutic for that

individual and --

DR. CASSELL: But do you have an ethical obligation not to? That is the question.

MS. LOWENKRON: That was going to be my next sentence.

DR. CASSELL: Do you have an ethical obligation not to?

DR. BRITO: I think with someone that -- someone that has good cognition and is able to understand, et cetera, and you are sure that that person understands what you are saying I think is sometimes up to the individual or the individual's guardian to make that decision.

DR. CHILDRESS: We will have one last question.

Zeke?

DR. EMANUEL: This issue between therapeutic and nontherapeutic is becoming pivotal and also the more pivotal it becomes the more hazy it is as I listen to everyone. Could you give me a sense for what you define as nontherapeutic research?

I guess here is the question: As an oncologist we give drugs and sometimes before we take lab assessments just to make sure and then we take lab assessments afterwards, and sometimes we do it even though we expect no changes. For example, we want to know whether the drug gets into the CNS. We might take a CSF sample. Now would that qualify as nontherapeutic, part of -- appended to a therapeutic procedure or not?

MS. LOWENKRON: You are going to have to run it by me one more time, the exact facts of it, but I think if I say one thing perhaps it is responsive to you because I think it is something I wanted to respond to the other gentleman, which is if you are talking about something that has the possibility of benefiting the individual in front of you when you have looked at all of the other alternatives, and there is a possibility of benefit, that is all that I am -- we started with that as the common rule definition. That was the definition in the regulations.

If there is a possibility of benefiting the health and well-being of the individual then it is in that category of possibly therapeutic, which is another reason that a lot of research is going to forward.

So I do not know if that is responsive. Maybe you have to run your specific example by me again.

DR. EMANUEL: Let's say we just want to know whether the drug gets into the CNS, to the central nervous system, and we are going to take a sample, do a lumbar puncture to get a sample of CSF where the drug is working somewhere else in the body. Is that nontherapeutic or therapeutic?

MR. CAPRON: Do you intend to do anything with the information vis-a-vis this patient?

DR. EMANUEL: Yes. No, not vis-a-vis this patient but you are collecting it because it might point out that the drug has other effects. Say on brain tumors or something.

MS. LOWENKRON: I think that is the example that Dr.

Oldham was using and I do not think that that is something that is therapeutic. If it is not -- and the key thing is what Professor Capron said of it being beneficial to the individual in front of you.

DR. MIIKE: If I understand you correctly, if you have an experiment that has a nontherapeutic arm and a therapeutic arm, you would not want that to go forward unless you could eliminate the nontherapeutic arm. If that is the case how can you ever -- once a drug is out there in the marketplace, don't you then end up in a situation in which you are going to -- how are you going to prove a drug for therapeutic uses when part of the nontherapeutic protocol on testing the drug is essential to knowing how it works?

So I am sort of faced with the ethical dilemma if I take your position that I can never ethically use the drug ever. I do not see how you could -- we end up in a position where we then are back in the old days in which you test drugs only in a very narrow population and then when the doctor gets it they use it across the whole range of people out there who need it.

So can you help me with that dilemma? If you are sticking to your position how do you help me out in the dilemma about subsequent wide use?

MS. LOWENKRON: Again recognizing that the issue is narrow to children because --

DR. MIIKE: Of course.

MS. LOWENKRON: Okay. And my response is that that is not -- that is the kind of research that is just not going to get done when you have that kind of research.

DR. MIIKE: How can you ever be sure about the drugs that you are going to use and how are you going to ever get a drug out there to treat kids if you have never allowed a nontherapeutic arm of a research.

MS. LOWENKRON: Well, I think that --

DR. CHILDRESS: This will be the last response. We will let you off the hook with this one.

MS. LOWENKRON: Okay.

I mean, I think, that part of the testing is done by -- it is done in adults, which is one of the answers, and I know that is not a satisfactory answer, and I know the pediatricians are totally groaning. And the other response is that it is done -- if that is the available modality and it is the only thing available for this individual then it is considered to be therapeutic. It is not -- there is -- I mean that is the line that the court has drawn and that is the line that I am drawing with respect to these nontherapeutic elements.

MR. CAPRON: Larry, I think there is a misunderstanding. The answer you just got is not the answer I got.

I understood you to say there is some treatment but it has a lot of problems and someone comes up with a new treatment and proposes to try the new treatment. If it is being tried as a

treatment even though it is research it is an acceptable "therapeutic" research.

DR. MIIKE: I know but she also said that there is a nontherapeutic research arm that could take that out. In other words, to disaggregate the whole research protocol so that you out what she would object to as the nontherapeutic arm.

MR. CAPRON: Well, the irony is, I gather, that if you are doing "therapeutic research" any normal assessment of the patient during that therapeutic research is part of the therapeutic research.

MS. LOWENKRON: Right.

DR. MIIKE: That is not what I heard her say.

MR. CAPRON: Yes, but that is what she is saying. That is, in fact --

MS. LOWENKRON: That is exactly what I am saying.

DR. MIIKE: What about lumbar puncture and PET scan?

MR. CAPRON: If it is being done as part of a therapeutic research.

MS. LOWENKRON: For that individual.

MR. CAPRON: For that individual, yes.

DR. CASSELL: It would be therapeutic.

(Simultaneous discussion.)

DR. MIIKE: Lumbar puncture and PET scan would be acceptable to you? I thought I just heard in your discussion that that is something that was not acceptable.

MR. CAPRON: That is when it was being done in the --

MS. LOWENKRON: In the context of --

DR. MIIKE: No, I want her to answer the question, Alex. I want her to answer the question.

DR. CHILDRESS: And this will be the end of this conversation.

MS. LOWENKRON: If it is done in the context of nontherapeutic experiments and it is considered to be greater than minimal risk then it is not something that can be done. If on the other hand it is being done for the purposes of therapy for the individual in front of you it is therapeutic research and can go forward irrespective of whether it is called greater than minimal risk.

DR. MIIKE: You would not be looking at the protocol and saying if this is not overall therapeutic research then you have no quarrel with specific parts of that research agenda. That is not what I heard you saying earlier.

MS. LOWENKRON: It is not what I am saying. I am saying that if --

DR. CHILDRESS: We will have to read the document. That is it.

Thank you so much for your help.

As chair I did not mind actually this going on as long as it did because we have already begun to do what we are going to

do anyhow. Namely we started talking about therapeutic/nontherapeutic. We started talking about how you think about risk and we started talking about advance directives and so forth. So actually this has been a very helpful discussion leading us into our serious and sustained discussion of substantive and procedural matters.

So I thank all of you, all four of you who participated in this on the T.D. case and we are grateful to you for sharing with us.

DISCUSSION: PROTECTING COGNITIVELY IMPAIRED RESEARCH SUBJECTS

DR. CHILDRESS :So we will now shift into thinking about how we want to do a report on recommendations. This has been a very important day in that we started out with a discussion of the whole question about placebo controls and other ways to establish difference. We have had some very important public testimony from a variety of sources about problems and also benefits in the context of research involving decisionally impaired subjects and then we had this very important discussion.

I think all that has happened today has helped and will help us move forward in coming up with some kind of report of recommendations.

Now let me just make a couple of points. One is and I mentioned this, this morning, before several of you were here. I think it was before Alex got here. As we are thinking about the time frame the National Institute of Mental Health is doing a conference on the 2nd and 3rd. I passed out information about it but it may not have reached you.

At any rate I think that is going to be very important for us to have the input from that conference before we try to wrap up a report. So it is probably better to think in terms of trying to have something ready in January if that is not a problem for people. That was one of the important things to mention.

DISCUSSION: PROTECTING COGNITIVELY IMPAIRED RESEARCH SUBJECTS

MR. CAPRON: The report on the incapacitated subjects?

DR. CHILDRESS: Right. As distinguished from the federal agency report which we will come back to later which we hope to have done earlier than that.

DR. BRITO: December 2nd?

DR. CHILDRESS: December 2nd and 3rd.

DR. GREIDER: That is this?

DR. CHILDRESS: No. That is the conference from back in May or June in Maryland.

DR. _____: I have the schedule.

DR. CHILDRESS: Oh, you do have a schedule for us. All right. Do you have the schedule?

DR. _____: Right.

DR. CHILDRESS: Good. Okay.

DR. _____: This is a draft of a schedule for that meeting.

MR. CAPRON: In December?

DR. _____: In December.

DR. CHILDRESS: And this will be clearer than what I had circulated earlier. Do you have enough just to -- are there enough copies to go around?

DR. _____: I think so.

DR. CHILDRESS: If not, we can have some more copies made.

DR. _____: If the machine wants to work.

DR. CHILDRESS: If the machine does. Okay.

Anything you want to say about it?

DR. _____: No. I understood that --

DR. CHILDRESS: He did this morning. So that is fine. Okay. But it seems to me that is important for those of us who can to take part in that and at least get the benefits of it as we try to finish up a report on recommendations.

We have been very fortunate in hearing virtually at every session, not related to cloning, about something regarding decisionally impaired subjects. So we have had a lot before us and most recently we have benefitted greatly from Rebecca Dresser's paper which has been now revised a couple of times and Jonathan Moreno's paper which was also revised a couple of times.

I thought we would use Jonathan and his draft of the issues if it is agreeable as a way to formulate -- well, as issues for us to begin to focus on so that we can see sort of where we want to take a report and where we want to come out.

Now, Jonathan will be able to continue working with us at least into the early part of the year.

John, is it okay if I make an announcement?

DR. MORENO: You may.

DR. CHILDRESS: I am just pleased to note that John Moreno will be joining the faculty at the University Virginia next year. He is John Fletcher's successor. So we are pleased about that. Since I took part in that I wanted to announce that to everybody.

But he will be discussing this issue, this set of issues, with us. So I am quite open to -- given the vigorous discussion we just had, which again I think helped move us forward, where do you want to start in this in thinking about where we ought to go and what else we need to do?

Alex?

MR. CAPRON: Two comments. One is in an amendment to what I said this morning. We were hearing initially, and the

question initially came up, when we were hearing about some research that took place apparently without federal support in a private or state institution some years ago, and we have had allegations of that sort of problem brought before us in written form as well.

We also heard, however, this morning about research conducted here at NIMH. The description of that research beyond the characterization of the quality of the therapeutic intent of the researchers, which I thought was mostly relevant since it suggested some credibility to the view that the individuals participating were being regarded solely as subjects and not as patient subjects whose long-term welfare was of any interest, that they were experimental animals for that purpose, but we heard allegations about the way that research was conducted such as the signing of dozens of consent forms at once. That could not in a million years be characterized as a process of informed voluntary consent.

We heard other statements about how people were brought into research.

While we cannot redress the first kinds of things we were hearing about where privately conducted research led to harm, we certainly should take note of and ask both from the researcher and from the Office for Protection from Research Risk for a response to these allegations.

If this is a pattern that has been going on at that institution it has to stop. And I would like to know whether the institution would regard it as an aberration. A once -- I mean, if their claim is that it is a false allegation. If it is an allegation that holds up, what OPRR will be doing about it and what the institution will be doing about it correctively.

Furthermore, I think that to the extent that we have documentation of any of these problems and can do at least minimal investigation such as asking for the other side to defend itself, it is perfectly appropriate in our report to convey to the public and to the president the seriousness of the conclusions that we come to by way of recommendations for change to use as examples any documented cases in which abuses have occurred.

It does not do much to come up with recommendations if there is not much behind them and if we have come to them in part because of the stories that have been told to us which we end up being convinced by, I think it is important that we share that information. And to the extent that it is something which is under our purview because it is not merely federally funded but federally conducted I think we need to get more investigation of the reliability of the reports that we have heard, and if they are, some statement of why that is a problem, what is being done about that problem, and why that problem is a window on to a larger problem for us, which we are then going to be addressing in the following recommendations.

That is the first comment.

The second comment is I think it would be worthwhile our

developing some kind of a taxonomy of the categories that these problems seem to fall in. There are problems that are problems of implementation of current rules. If -- as an example, that multiple rapid no chance to think about it signing of, in effect, blank consent forms or consent forms being signed after the research has already gone forward. That -- those are problems which are not problems that we can ignore simply because we already have rules against them.

Those are problems which indicate the inadequacy of the implementation process and they ought to be of great concern to us because I cannot believe that if they are substantiated that they are limited to this one category of patients.

Then there are the problems that come from the fact that the 1978 recommendations of the National Commission have never been implemented nor revised adequately to meet whatever objections were raised to them.

We are 20 years after that date when they addressed that. It seems to me that one thing I at least would conclude is that the fact that there was objection to what the National Commission did and this was seen as being a subject which was in some sense kind of intractable, not only has probably prevented some valuable research from going on because legitimate researchers are afraid they do not have a framework in which they can do it, but has allowed other research to go on which people thinking that there are protections as the judges in New York think there are protections when there really are no specific federal protections for these incapacitated subjects.

Some of the problems which have been alleged to have occurred I think have arisen because of that and we need to draw up some firm conclusions and then, since we will not be going out of business the way the National Commission did as soon as those recommendations were issued, we need to be in a position to follow up. But that will require us to resolve the questions that were so difficult for them.

Mostly they have been illustrated, as you said, Jim, in effect, by this last panel. This tension between what happens when you start doing some nontherapeutic things with people who cannot consent or whose consent is arguably not valued because of their either mental status or their institutional status.

But we have got to develop that line as well as criticizing the failure of implementation of existing regulations.

DR. CHILDRESS: Eric?

DR. CASSELL: I think I want to add to that. We have heard this morning there probably are regulations that cover virtually every one of those things and that they are already in place or they have been written before and yet not brought forward. The abuses occurred in people who know very well what they are supposed to do. The people who had those consent forms, they know very well that that is not really a consent, but they are good

persons, true, and anybody wants to do this research and so it is really all right to do that because there is no fundamental understanding of what that consent means. That is not just a failure of form. It is a failure really understanding what a consent is all about on the one hand.

So on the one hand we have people who just do not really get it about what they are doing and the second thing are failures of commonly accepted relationships between care givers and patients, matters of trust, matters of concern and follow-up, which everybody accepts. Everybody accepts are supposed to be minimal standards of care and yet they break down.

I do not want to be cynical but I do not believe we heard exceptions today. I have a feeling we heard something that is awfully common and not getting less common.

So our task is on the one hand to regulate with better regulations but on the other hand to solve the problems of failure of trust and beneficence, you know, and figure out a way that might, in fact, do that because as it stands now there is not a way.

With all due respect to wonderful seven year crusades against something that kind of sharp restraint of therapeutic/nontherapeutic when, in fact, in the real world it does not divide like that, all that does is make people sneak around and figure out another way not to follow the rules.

So I would like very much to see us move forward in both of those directions.

DR. CHILDRESS: Diane?

DR. SCOTT-JONES: I have noted three issues that I think we should cover in this issue and I think all of these have broader implications but I think they are especially important in our discussion of the cognitively impaired. The first of these is the role of the IRB and in particular there are a few things that came up. One is the composition of IRB's and whether there are persons who are on IRB's who might function in a sense as outsiders to the research process.

A second, IRB's often decide what is risk or minimal risk and there needs to be a lot more discussion of the definition of risk and minimal risk because those are often decided in relation to the risk of every day life or the risk of commonly accepted procedures. So we need to have more discussion of what risk and minimal risk actually mean.

Then the third concern in relation to IRB's is whether there needs to be some monitoring process that is more extensive than IRB's commonly do. Especially in longitudinal research there needs to be revisiting of the consent in a meaningful way if a study extends over a very long period of time.

I think here the education of researchers actually -- who are actually responsible for seeing that the IRB's decisions are carried out is really important because nobody really monitors researchers to see whether they do what they have agreed to do in

the documents that they submit to the IRB's because you cannot really monitor researchers in a meaningful way and it would not be appropriate to. One needs to rely on the researchers themselves to believe in what they are told to do by an IRB.

Then the third thing that I think we need to pay attention to is -- well, maybe I actually have four things here instead of three. The third thing is --

DR. CHILDRESS: I thought it was all my counting for a moment.

DR. SCOTT-JONES: -- this issue of placebo control trials and whether we need to think about both the ethics of that and the scientific usefulness of that. The example of what to do in an emergency when a person is in a blinded study was really quite striking when we heard about it today. So we need to do a lot of thinking about placebo control trials and their function in research.

And then the last thing is we need to do a lot of thinking about this distinction between research and therapy and the relative importance of treatment in research in projects that do have a therapeutic goal.

DR. CHILDRESS: Bernie and Trish?

DR. LO: Yes. Just to add to what I think is a very good list of very difficult issues that we need to deal with is the notion that research really takes place over time and as currently the guidelines, the safeguards are constructed, we only look at the onset. So it is informed consent to any of the trials IRB approval of the protocol.

I sit on a number of data safety monitoring boards for clinical trials and as everybody knows when you do a study a lot of things happen in the course of the study. We heard from the patient's family point of view some of the bad things that happen and some of the problems in terms of side effects when you are on a blinded study or second thoughts about wanting to disenroll from the study but feeling you cannot because you want to get some information and they will not give you information unless you stay in for the whole trial. Those sorts of issues.

It seems to me that in between saying that we have to rely on sort of the virtue of the researchers and saying we have to sort of look over the shoulder every step of the way, there are intermediate steps, and I would just like to sort through something like an ongoing committee that reviews a study, a longitudinal study, maybe ones that raise red flags because they have as patient enrollees people of questionable decision making capacity or children.

An independent committee that could certainly have among its members people who are either afflicted with the condition or family members or community representatives or something to overlook the study as it proceeds and to look particularly for such -- not just the medical complications and sort of the dramatic results that

would lead you to stop the trial early, but also maybe to look into how is the consent process going. Is there a good attempt made to sort of inform patients and family members as the study enfolds.

I think when you get involved as a researcher you really get involved with wanting to do a good job in the study and it is very easy to let other things sort of fall out of your view. It is sometimes a lot easier when an independent board looks at things and says, "We really have got to have a heart to heart talk with the research team," and just sort of make them aware of the issue and to think through with them, help them think through how they are going to address it.

I would like to try and -- and that need not be onerous. I mean we always get complaints that, you know, why do they have to present every six months to a data safety monitoring board but I think by and large in big clinical trials it is accepted. It is a plus for the research and the research team to have that independent oversight. So I think we have to not just -- and we can all think of additional regulations that will kind of at least on paper address these issues. But as several have pointed out, we have regulations that cover most of the things we heard about this morning. They are just not enforced. They are not carried out for whatever reason.

So I think we have to craft something that tries to address the issues and tries to address them in a way that gets the researchers involved in solving the problem as opposed to saying, you know, we are going to have someone else take care of it for you. But it has got to be over time and, you know, I think we have to I think get away from the idea that consent and IRB, which are really the keystones of current protection of human subjects, as only taking place at the onset of the study.

DR. CASSELL: You know, Bernie, you used the words that researchers want to do a good study and that is why things fall by the wayside because really watching over those consents and watching over those patients is not part of a good study. What is the good study is getting good data, right. So that the other part that involves the subjects as subjects get left to the side.

DR. LO: All too often it is enrolling the patients and getting the data. On the other hand a really good researcher knows what makes a good study is that human contact between your team, the patient and the family. I mean any person who does clinical trials says the key person is your research nurse who does the extra mile of making that human contact with the patient so they keep coming back on time and on schedule because, you know, you send them a birthday card, you always know to ask about the things that they care about, how are you doing. It makes a difference to the subjects and, in fact, that is why a lot of people enroll in studies for that kind of interaction and contact.

DR. CHILDRESS: Trish and Arturo.

DR. BACKLAR: But it is interesting what you are saying.

You are pointing at exactly the problem of what many people today talked about what pushed them into a research protocol was their desire for care which they were not getting in the social -- in the communities that we live in. If we only look at research as something quite different out of which people are coming into you have to look at the whole picture.

We are looking when we look at people with cognitive disabilities, people with serious mental disorders, we must remember that this group of people just like people with AIDS is looking for some kind of treatment. We go back to this problem which we went through over and over with this attorney of what is therapeutic and what is not. I think that we have got to make a definite -- we have got to take the word "therapeutic" away from research.

Research is by description hypothetical. We do not know if it is going to be therapeutic if it is research. It may be or it may not be. Our way of identifying risk is something different necessarily from therapeutic and that is why risk has to be looked at very carefully.

But going back to the analogy between people with AIDS looking for treatment and going into research, it is extremely different in that population than the people with serious mental disorders who may not have the abilities to discern and their families may be so anxious they also, even though they may not have cognitive impairment, their desire for care and for help for their relatives is so enormous that they willingly put them into a situation to after which they are extremely sorry and as we heard today feel very guilty.

DR. SCOTT-JONES: What I want to say now is related to what Trish has just said. It has to do with this issue of what is research and what is therapy and what is the relationship between the two. If we believe that participation in research is genuinely voluntary and not in any way coerced and that a person enters into a research project with information that you have given your consent on the basis of information about the study then you would have to raise a question, at least raise your eyebrow, about some of the studies that are being done.

Because if it is the person's only option for care, your only option for treatment, then that research participation is no longer voluntary but it is coerced. You are entering into it because you need care and it says a lot about the availability of care to citizens in our country when they have to participate in research in order to get care. It is very troubling if that is the case that a person who is only seeking care must participate in research to get that care. Then research is no longer voluntary and lacking coercion. It is really very troubling. You cannot separate then the issue of access to care from participating in research.

DR. CHILDRESS: Arturo, before I turn to you Zeke wanted to respond, I think, on the coercive part.

DR. EMANUEL: I want to respond generally but after

Arturo. He has been waiting.

DR. CHILDRESS: Okay.

DR. BRITO: Thank you. One comment that was made this morning that -- I made a whole list of broad categories. I am just going to touch on the ones that have not been touched thus far. One of them being that the commercial vendors seem to be -- this is through the readings too -- override or take priority of individual's rights when drug companies -- this just is not -- this applies to mostly privately funded research but sometimes we forget that privately funded research can go on as we saw this morning at academic institutions. I think that is something we should address.

And then when you have an organization like the OPRR that is entrusted to investigate these and their hands are tied because of funding or limited resources I think that is something we should also address when we make our recommendations, either proposing more funding or, you know, who knows, taxing the pharmaceutical companies when they do the research and putting that money to the investigations, et cetera.

I had some other points that Diane just went over about the voluntariness of the involvement in research. The impression I am getting is that most people with mental disorders that involve themselves in research are doing it usually out of desperation and not for altruistic desire.

Then the other major point is the need or apparent need for autonomous primary health care provider that is not involved in research for research participants, particularly with mental disorders.

And we went over the IRB structure and role.

Oh, and then the responsibility of the researchers to follow up on the subjects. I think that is something we should also address at some point long after the research protocol is done.

DR. CHILDRESS: Zeke?

DR. EMANUEL: Yes. I guess -- and I apologize for not being here this morning and getting the full impact of many of the problems which I know are egregious in many cases. I guess I would plead that we keep the report focused on things that are going to have action in a broad context, not a particular research protocol, not for investigating a particular problem. Because it seems to me those are appropriately done at different places and that our biggest benefit is can we lay a framework that is going to be applicable for federal and beyond federal for privately funded research as well.

Therefore, I would dissent from some of the suggestions here by some of my colleagues just because I cannot agree that we should investigate NIMH and all of that. I just do not think that is appropriate.

The second thing is I think we have to be a little realistic about the contacts in which a lot of this occurred. We cannot control the fact that access is limited and that sometimes

some people may feel that coming to a research center or getting on a research protocol is their only way of getting help there.

Would that we could change that just by this commission voting it.

It seems to me if we are going to be effective we have to deal to some extent with the reality to which it occurs and, you know, unfortunately in the area of mental health benefits those benefits are probably under more sheets than anything else even for those of us who are insured. But I think we are not going to be able to solve that problem and the best we can do is provide protections in the research context and rethink that protection system in the ways that I think have been suggested.

Is the informed consent going right? Do we have ongoing review rather than just a stark review? Is there a way of rechecking with the people about their continued consent? Do we have education -- appropriate education of investigators, et cetera? Those seem to me to be the right context. The bigger political context unfortunately we cannot change although we could say something about desirability but Lord knows that is not going to happen so fast.

DR. CHILDRESS: Alex, did I see your hand?

MR. CAPRON: Yes.

DR. CHILDRESS: Then Trish and then Bernie.

MR. CAPRON: Yes, I think that the question that Diane raises is one that we should have on our topics to address and I think I am somewhere between her view and Zeke's. Again I would want to try to tease out the factors.

The thing that made the Willowbrook story so egregious was that the very same people who controlled the therapeutic modality, which was treatment in the state institution, which was thought to be the appropriate location for the patients who were going in there, subsequent views I think have moderated that view as to whether that is the appropriate intervention, but at the time that is what parents thought they should be doing.

They made it clear that they had another objective, namely research, and in order to have subjects for that research the door that they kept open and the part of the facility which they ran where hepatitis was not endemic because if it had been endemic they could not have been doing their research study, they were able to keep the conditions there sanitary enough and keep the patients from infecting each other so that they could do research. They said to desperate people, "This is the only way you can get the treatment we can offer and, indeed, it will be much better treatment than the people who are in the regular part of the institution are getting."

That seems to me different although I am not sure that the difference ends up being that important but it does seem to me different in evaluating it from the situation in which people are faced with the reality that there is no other good treatment available whether their condition is a mental illness or a physical

illness.

Someone has developed a potential treatment and are saying because it is not yet approved the only way I can offer it to you is in a research protocol and, yes, one's choice to go into that research protocol is constrained but I am not sure that it makes it -- that it is appropriate to say that it is involuntary in the same way. I mean after all most of us would not take any medical treatment if we did not have an illness and so there is a sense in which our choice is constrained, either we take the illness or we take the treatment that is available or we suffer the illness.

I think that if we explore this issue and if we do draw a difference with mental illness we have got to be very clear what it is about it.

Here I am concerned that we not confound our two concerns. One concern is that at least some of the people are not able to really give informed consent having nothing to do with this issue of constraint. It is just that their mental condition renders that difficult. And the additional overlay is that the people we would usually turn to as surrogates for them themselves are under enormous pressure and may themselves not think as clearly as they would if the question is should my child have a cancer treatment because they have not -- it is not suddenly that now the child has cancer. It is that the child has had this mental illness for months and years and years and they are at their wits end as to what to do.

But that is one problem and I think we need to keep that separate from this question of constraint because after all the constraint issue would be equally true for a person with an otherwise untreated illness of another sort. When they -- maybe there is a sense in which when they are compounded we have an extra problem and I am perfectly willing to recognize that. They are certainly compounded when the person is already in an institution and has all the constraints that come with being dependent on people and not having the same source of support as they would have and so forth.

I am getting a vigorous head shake from Trish but I want to finish the talk.

So I think you are right about the topic. I also think that if we are looking for topics that Jonathan's paper for us has a number which I would want us to directly address and one of them is this basic question of whether the therapeutic -- excuse me, the mentally impaired or the mentally incapacitated are simply out of bounds for research, period.

Certainly here there is something worthwhile about differentiating nontherapeutic research from research with a therapeutic intent. I mean I think we ought to reiterate the views that the phrase "therapeutic research" should disappear but it is not just the phrase that is the problem. It is that there is a difference between the presentation of something as being potentially beneficial for you and then we care about how accurately

the potential is described. Is it over sold or not? And something which is unrelated to any benefit for you. You are simply a convenient subject.

We can certainly draw the line on saying that the latter has no place in mental institutions. Just the fact that your life is controlled and your diet is supposedly controlled and so forth and, therefore, we could study X, Y, Z with you which has nothing to do with your illness, that line should clearly be drawn as being beyond the bounds it seems to me. But that does not answer the difference then of what do we do with things which have a therapeutic intent even if we are careful to say, "Well, it is not therapeutic research, it is research on treatment." It is not yet treatment, it is research on a treatment.

DR. CHILDRESS: We are going to need to take a break a little earlier just because so many in the genetics area are going to have to depart. I have three people on the list. You are not forgotten, Trish, so you are next. But I would like for Trish, Bernie and Alta to state their's very quickly. Then what I want to see is if there are any people who will be departing for the genetics subcommittee meeting who have some things they would like for us to be sure to keep in mind when we come back after the break and spend a bit more time sketching out how we will proceed.

So, Trish, Bernie and Alta.

DR. BACKLAR: One more thing that is procedural. When we finish with this, those who are going to the genetics committee, at 5:00 o'clock we can come back here and have half an hour more.

DR. CHILDRESS: If we are still going. We have not made a commitment to stay until 5:30. We have that time if necessary.

DR. BACKLAR: Those of us who are going really apologize because I personally very much wanted to hear what Bill was going to say and I will read it in the transcript.

I just wanted to say one thing and that was I did not talk about the social situation as our addressing the social situation but we cannot look at the protections we want in research without understanding that social situation which brings me to what Alex pointed out here, which is that in many ways this population is still an institutionalized population. It is not within an institution but some of the things that we looked at when they were institutionalized remain. They are kind of a pool of people for research because there is not much else going on. One has to be awfully careful because of that. That is all. That is why I was shaking my head.

DR. CHILDRESS: Bernie?

DR. LO: I just wanted to suggest that a lot of the issues that we have seen very starkly drawn in this sort of mental health or persons with questionable decision making has to also apply in all other clinical research. So all the things you are seeing, people feel they have no other alternatives, they are desperate, their families are about to give up, the doctor who is

the only doctor, the best doctor in the area, also is the big researcher. It applies to AIDS. It applies to cancer.

This idea that people with depression are particularly likely to be deluded, have a delusion that it is really therapeutic for them even though they are trying to tell you it is not therapeutic. You know, I can talk to AIDS patients and explain this is not going to help you, it is going to help the next generation, and they go away thinking, you know, he said that but, you know, I really know that deep down this is going to somehow help me.

I am just afraid that one of the -- there is sort of a natural sense that certain research ought to go forward and if our categories do not line up with intuitive perceptions people will milk the categories. So what will happen is if you say as long as there is therapeutic potential it is okay but if it is nontherapeutic when subjected to such a restriction it basically will not happen. People start to stretch the definition of what is therapeutic potential. Well, I will do this extra set of tests. Maybe it will show something. I am not expecting it but if it does you will certainly benefit from knowing you have got this or that.

I think people will just try and make everything sound therapeutic and that is just going to compound the problem by giving our core of patients yet another reason to think that it is really for their direct benefit and not for sort of scientific mental health.

DR. CHILDRESS: Alta, Harold, and then anyone from the genetics subcommittee who will be leaving.

Alta?

MS. CHARO: First, I want to apologize if this has been said by somebody else. I got diverted in the hallway and missed the beginning of the discussion.

I feel like no matter how one goes through the list of the particular procedures that are offered up as possibilities for change here that you are going to run the risk of either protecting too few people and having some number of people enrolled who should not be enrolled and some number of people who are abused who should not be abused, and that you will do that because, in fact, there are some impetus here to speed up the rapidity with which you do the scientific work. Right? You loosen the protections, science is faster. I mean we are seeing the same kind of debate now in a topic we have not touched on today which is the one about the placebo controlled trials with perinatal transmission of HIV, right?

The other possibility is that you in a sense over protect. You protect too much. Too few people get in. Science is slowed. And the secondary allegation has been that a lot of people who want access to experimental therapy do not get it.

I would like to first of all urge us not to take that second concern too seriously because I do not think we should be aiming to make the research arena the place where people get therapeutic care. I think there is a fundamental structural problem

here. I think a lot of the stories this morning about betrayal came directly from the fact that people were entering these scenarios under the impression that they were going to be getting therapeutic care and that is simply not what the investigators had in mind. So I do not think we want to try to create a system that is amenable to people getting therapeutic care in a research context. But the scientific issues are real.

But we do have to kind of figure out which way the errors are going to go. We are either going to protect too many or too few and we have got to make a policy decision about that because from that flows all the decisions about the procedural items.

If you got stricter -- if your policy thrust is that you are going to be very, very strict, that high risk experiments do not pose a direct -- do not offer a significant direct benefit to the subjects are going to be prohibited, so you have eliminated the riskiest of your experiments and you can afford to be loose around your procedures and you do not necessarily have to come up with elaborate ways to have consent monitors, independent consenters, double checkers on the IRB's, et cetera. If you want to try to expand the trials to include those kinds of high risk experiments with very little benefit then you really do have to come up with an elaborated procedure.

But I think there is an initial policy thrust that has to be determined in order to help then drive the decisions about the procedures. Taking them on their own, I think, may force us to refight these arguments about the policy thrust on each item.

I am not advocating one position or another on the policy thrust but I do think we need to put it on our agenda more explicitly.

DR. CASSELL: Harold and then Tom.

DR. SHAPIRO: Some of my comments are very similar to what Alta just said and I will not tarry that further now and we can pursue that at another moment in time. But I want to return to something that occurred to me as I was listening to Bernie's remarks and that is that I think we do not do ourselves a service to draw some of these distinctions quite so carefully. I think it is quite the reverse. If we do not draw them so carefully we are more likely to understand what it is that is useful to do.

So these distinctions between vulnerable and nonvulnerable, therapeutic and nontherapeutic, minimal and nonminimal, these -- really none of these get to the heart of the problem. They are not trivial distinctions by any means but they are not really at the core of generating a solution to our problem because they appear -- whatever problem appears in the vulnerable populations appears also with nonvulnerable populations only in a different -- with a different face on it.

So it seems to me that as we go ahead we might not try to make quite so much of these distinctions. They are important in their own way. Certainly they are distinctive problems in certain

situations. But I think that the basic issue appears in all these populations and we have to think about that as we go through these various subjects.

DR. CASSELL: Tom?

DR. MURRAY: Just a quick response to Alta's point because I think Alta is right at some level we do have to make a policy choice. Policies are never perfect. They will end up either under protecting certain individuals or -- I am not sure over protecting is the right word but, you know, sort of harming -- creating a long-term harm that really does not advance any public good.

MS. CHARO: Right.

DR. MURRAY: And could prevent certain research from taking place. You cannot get it perfect. But what you can do, I think, is narrow the error bars there. What I heard from stories today persuades me that we have a long way to go at least in some research programs at some institutions in such things as accountability. So if you could think of measures that would increase the accountability of the institutions and the researchers you could actually enhance both those goals.

Now the intelligibility of the research -- and that is in part what is said on the consent forms but that is only a portion of what makes a research project intelligible -- and providing say opportunities for feedback by subjects and families of subjects if they feel there is some problematic element in the research.

So there are things we can do that, in fact, would I think push towards both of those desirable goals.

Could I just add, Jim --

DR. CHILDRESS: Sure.

DR. MURRAY: -- when we adjourn it is going to take a few minutes to scramble out of here for the genetic subcommittee members. It certainly is going to take a few minutes for me. We will convene right at 3:10.

DR. CASSELL: Exactly at 3:10, right?

DR. MURRAY: At 3:10.

DR. CHILDRESS: Okay.

MR. CAPRON: Jim, could I just add --

DR. CASSELL: Sure.

MR. CAPRON: -- Harold, I agree with you that every time you end up drawing a line then what becomes important is the margins on both sides of the line. But let me give you an example of the kind of thing I had in mind when I was talking about saying something is nontherapeutic.

If Revlon wants to test a face cream to find out whether it causes allergies they could go out and recruit people in the community or they could say to the state mental institution you have got 200 people in there, we will give you so many thousands of dollars for doing this, and we will give a nice little set of cosmetics to anyone who participates if you will let us do this.

Now it is probably no, yes, or whatever, but it is not therapeutic. It has nothing to do with the reason that these people are getting treatment.

I would -- hmm?

MS. CHARO: Nothing.

MR. CAPRON: Nothing? I would regard it as an example of a nontherapeutic experiment and probably one which I would say, "Go do it someplace else." There is just the perception that people rounded up -- have been rounded up and put in a hospital. I mean they are just guinea pigs at that point. I mean, in fact, they cannot even do this on guinea pigs because the people for the Ethical Treatment of Animals will not let them do it. Rubbing in rabbit's eyes the way they used to, to get the same result, so they now have to do it on people. Fine. I have no objection to protecting the rabbits but let's protect this -- I think there are some groups that are more vulnerable.

DR. SHAPIRO: I do not doubt that there are some groups that are more vulnerable. I agree with that. But I think that is a harder line -- all I was trying to say is it is a harder line to draw than one might think. The people are vulnerable for all kinds of reasons. Some are in prison and some are in the military and some are --

DR. EMANUEL: Poor.

DR. SHAPIRO: -- poor. Exactly.

DR. EMANUEL: Who is Revlon going to get? They are going to give $50 to the poor.

DR. SHAPIRO: And so all I am saying is not that this is not important, I think it is important. It is just a question that -- I do not want to make these lines too sharp, that is all. That is all I am saying. I agree that it is useful.

DR. CHILDRESS: All right. Well, we will take a break and we might as well start again at ten after. The Human Subjects Subcommittee will move forward and we will talk about how to wrap this report up. We will then deal with the federal agency report.

Those who are going to be at the Genetics Subcommittee meeting please get to us, to me, to Bill Freeman, any suggestions you have regarding the federal agency report. We really have to move forward with that.

(Whereupon, a brief break was taken at 3:01 p.m.)

DR. CHILDRESS: I would like to make a proposal that I mentioned to a couple of people at the break and for me the rationale for it has become even stronger as the day has gone on so I will make it now and see what you think and then return to the discussion of possible directions for a report.

I think that given what we have heard previously as well as what we have heard today, given the points that people have made today and on other occasions, given the background material that has been developed, particularly Dr. Dresser's paper and Dr. Moreno's couple of papers, that we are at a point where it would be useful to

get a couple of volunteers or if necessary draftees or conscriptees, to work with Jonathan and me to come up with a draft. He has already drafted a fairly strong or a newer version of a paper of his for a historical perception as to how do we get to this point which I think is an important part of this discussion. But that we really need now to take those papers that have been prepared and sort of put them in some kind of form for us then to deal with or say, "No, that does not capture it. No, we cannot go in this direction on the thing about risk or minimal risk or more than minimal risk. Or we cannot go in that direction on advance directives."

So I would like to offer that as a proposal and then as part of that, of course, there is a request for volunteers and we are interested in voluntary informed consent and all of that.

What do you think?

MS. CHARO: Before you get to the consent can you give us the informed?

DR. CHILDRESS: Well, the informed --

MS. CHARO: Like the time frame that you are talking about because that affects whether or not --

DR. CHILDRESS: Sure. Okay. Going back to an earlier part of our discussion we would like to move the drafting along quite well but not put anything in the final form until we have had an opportunity to participate in the conference on December the 2nd and 3rd. So shoot for something in -- closer to final form, a penultimate draft or whatever, some time in January. I do not recall our meeting scheduled for January but that would be at least what would strike me as a possible and plausible framework.

MS. CHARO: And are you looking for a coauthor or a reviewer, or both?

DR. CHILDRESS: Oh, we would assume that everybody would serve as reviewers at, you know, some point once we get something in shape. But a couple of people to really --

DR. MORENO: Write I think is the operative word.

MS. CHARO: Jonathan, you have got guts.

DR. SCOTT-JONES: Are you asking for volunteers to volunteer now or to call you?

DR. CHILDRESS: Oh, you can tell me later but if somebody would like to -- I would welcome the volunteers now but is this a direction that makes sense to you for how to proceed? Obviously given our previous discussion there are some things that we will have considerable division on. However, I think the discussions we have had been useful for indicating where the key issues are and then we can try to sketch ways to deal with those that obviously would not require then our very careful scrutiny.

But I guess my sense is that we are not going to -- that we really need to move to that stage if we are going to move forward with a report and recommendations.

Arturo or Alex, either one?

DR. BRITO: I was just going to ask would it be a little

easier if you could divide it up into subsections and then people could contribute in different ways?

DR. CHILDRESS: That is going to be one of the issues and maybe our committee could work on organizing it. There is a clear historical section but beyond that it is not as -- one of the big questions is sort of how you put it all together then.

DR. BRITO: Exactly.

DR. CHILDRESS: So that -- I think it is not something that we could -- we could not lay it out say the way we did the cloning report by saying very clearly, you know, there are scientific issues and then there are other legal, policy, ethical and religious or this does not fall out that way, I think.

DR. BRITO: Not as clearly. For instance, this morning or just now we just discussed some of the more basic concepts that we are going to probably undertake or at least some of them and until we decide which of those we are going to do I think it is hard to say, at least for me, whether I could volunteer for this because I am not sure I would be able to write about some of them but some others I think I could.

Are we still talking about dealing with the cognitively impaired at this point?

DR. CHILDRESS: Right.

DR. BRITO: By January.

DR. CHILDRESS: Just that population, right.

DR. BRITO: I guess the issue does not quite -- it does not divide itself out as nicely.

DR. CHILDRESS: Alex?

MR. CAPRON: This is a general comment about the work of the commission but since we are at that point on this report I think it is difficult for a variety for reasons for us to try to repeat with these other ongoing topics we have what we had to do because of the force of time with the cloning report. While it is obviously desirable for people who have special interests to submit ideas and draftings if that is useful.

I understand we have the resources both in terms of hiring some staff members and also to contract for services as necessary. I think there is actually for a group that is going to be working together an advantage to divide the staff function from the commission function. The commission function is to consider an issue, outline what the problem is, outline the potential proposed solutions to the problem, and to review attempts to put that into final form.

I think it in some ways makes it harder to have a commission process in which what we are looking at are our fellow commissioners' work primarily. It constrains discussion and critique. I mean when I think of the advantage I believe we have in responding under federal agency mandate that we have three -- actually more than three I guess, but three principal people who are on staff who have been doing that work for us. It gives me a very

different feeling about my ability to comment on it and to -- and the fact that it has collective ownership of all of us and not that of any particular person.

So that as agreeable as in many circumstances what you describe might be and as appropriate as it is in some settings like the National Academy of Sciences where committees have relatively small staffs but where everyone is sitting around the table and is usually equally knowledgeable about the particular narrow topic that is being looked at, here we have huge differences among the 18 of us as to how much we know about any of the topics. Therefore, the extent to which any one person would basically be in a position to do that writing and then to sort of have to defend it or say, "Well, it is because of my superior knowledge of this that I know this is right."

So I actually do not favor the approach that we are about to take on this. I believe we should gear up and get people in-house or contracted.

DR. CHILDRESS: See, I think that the reason for making the proposal is precisely just what has happened. Not that it is the only proposal but just as I think on the decisionally impaired we are not going to make any progress until we get some concrete stuff out. So I do not think we make progress in just sort of throwing out --

MR. CAPRON: Okay.

DR. CHILDRESS: I made a proposal and I think you made an excellent counterproposal and I happen to agree with it more than I do with mine. But that it seems to me the way discussions go.

DR. BRITO: Maybe the volunteers you need from the commission right now is just to make a decision about -- well, it should be everyone actually giving input about what it is exactly -- what issues we are going to be tackling and what can we realistically do before January, and then like Alex said --

DR. CHILDRESS: The issues we are going to be tackling -- that is why we looked at Moreno's paper.

DR. BRITO: Yes.

DR. CHILDRESS: There are 14 issues that need to be tackled or at least we need to talk about whether we think some do not need to be tackled. So it seems to me that -- and again this is also related to Rebecca Dresser's point so we have a good body of material to work with. Jonathan and I have not had a chance to talk so I do not know in terms of his time frame over the next three months, let's say, and then Alex's point about getting some additional help for him as needed to work with us.

If everyone agrees with Alex's proposal I am quite comfortable in going that way. We are such a small group I do not see any need to have a formal vote.

MR. CAPRON: I have raised this with Harold and he says we have the money to do it.

DR. CHILDRESS: Okay.

MR. CAPRON: Staff or part-time borrowed people or consultants, contractors.

MS. CHARO: I am just not sure I completely understand what you are suggesting. That is that we get additional staff hired to work with Jonathan to produce the draft.

MR. CAPRON: I would think if Jonathan were full-time from now on he probably would be enough staff to do what we need done. He is not and he is time limited. He is not full-time now and he is time limited in terms of these new obligations he will have.

DR. CHILDRESS: Can I just clarify one thing? You said staff. I think Alex would be as satisfied with a contractor who would be able to --

MR. CAPRON: Kathy. An equivalent of Kathy Hanna.

MS. CHARO: One thing though --

MR. CAPRON: But doing more of the original work, not just the --

MS. CHARO: -- because I think in light of what was presented this morning and the conversation that took place afterwards of which I only heard a half, but I actually heard things that I think are worth deciding. I do think that there still might be a role for those of us who can to draft -- I do not know exactly how to phrase it -- summaries of things that indicate directions, preferences about the resolution of certain issues, ways of combining some of these issues that are not -- that are currently broken out completely for the purpose of clarifying them so that there is a little more direction given. Otherwise you are leaving --

MR. CAPRON: I agree.

MS. CHARO: -- Jonathan and anybody else that you are working with just a laundry list and they can -- they can bolt it up back again to Rebecca's paper and it still will not get us moving forward.

DR. CHILDRESS: Actually this is what I had in mind except Jonathan said right. He was -- I was not thinking as much of our writing in the strict sense as working with Jonathan to shape the direction. So actually I think we are pretty much in agreement about -- if Alex agrees with this -- the role of the subcommittee in working with whoever is involved in the writing.

But the shape is not clear. We assume there needs to be a historical section and I think there does. So whatever has happened before why are we at this point from the previous proposals and failures. Beyond that I am not -- there are so many different ways we could shape this.

MS. CHARO: In that case we will free to send you memos with however many pages it takes to lay some of that out but I would also encourage you to use the certified question model to certify questions to the commission where direction has not been given yet and you need it in order to proceed.

MR. CAPRON: Are we going to do some more of that right now?

DR. CHILDRESS: We are. I just thought coming back from the break that it was useful to go ahead and get this out of the way and then come back to the --

MR. CAPRON: Yes, fine. I thought Alta was afraid that, you know, we were done with the subject and she is going to have to do it by mail but I think we are going to have some discussion.

DR. CHILDRESS: We tried to build in enough time. Let me just ask the subcommittee, we have close to two hours and I think that is more than enough to cover some new business at the end and to deal with the federal agency report. But in proposing it that way and offering that is what I think at this point, that is going to depend in part on what you think and how much time you think we need for the federal agency report. I would say a minimum of an hour and maybe even longer. But that would still leave us a fair amount of time to talk a bit more.

Any sense of that?

DR. CASSELL: That is fine. When are we going to pick up on the IRB's?

DR. CHILDRESS: Okay. I am not sure you were here this morning when I indicated what I take to be some of the next steps and things that we have talked about and agreed upon sometimes as a subcommittee and sometimes -- no, I think all of these actually as a ratification of NBAC as a whole -- and just sort of put them in some kind of order.

We now have Celia Fischer's paper on vulnerability. We are also in discussion with another person about a community paper. And there are some philosophers working on vulnerability with that we have had some conversations with and we may get something there. So this is kind of the direction. Part of Harold's point, part of something we talked about at the very first session, is how you go about thinking about relationship, all the relationships, and vulnerability in those contexts.

We could talk, for example, about Fischer's paper at the next meeting and perhaps have at least some direction on these other two though we are not going to have anything final.

OPRR, we have two contracts. A pro/con contract. Pro in keeping current location and con of putting it somewhere else. Those are I think now -- did you say not quite official? She told me they would not be official by today so I may not be at liberty to say which persons are involved. But anyway we have two people who are involved in that preparation and we now need a third which we do not yet have to talk about the possible role of OPRR in dealing with privately funded research. We can come back to that in a moment. So far we have two.

International discussion I mentioned this morning. It seems that these -- if we are talking about private -- you know, things seem to happen on days we are meeting or next to the days we

are meeting. The New England Journal of Medicine articles today which were put in people's table folders. The discussion we had last time about international research. This is clearly an important topic that we need to attend to. And Bill Freeman has prepared, and it is also in your stack of paper -- parenthetically, we are all familiar today that we are just about to be overwhelmed by paper.

DR. CASSELL: There are two more inches. We are overwhelmed.

DR. CHILDRESS: Okay. I agree. I think it really is. But at any rate somewhere in this stuff Bill Freeman has prepared a very nice discussion of a set of issues including connecting the debate about placebo, which we started with this morning, with a discussion of international research since actually those are closely connected in some of the critical cases.

One possibility would be at the next meeting on October the 19th to see if we could actually have responses along the lines we were talking about last time and perhaps even have contract papers of the thought kind we were asking for in OPRR from sort of opposing views, people who have worked in the area of research or bioethics, offering some contrasting views on that but from sort of academic scholarly side but clearly taking positions.

Then IRB's, we had talked long ago about waiting until we got at least preliminary results from the Charles McKay and Office of Inspector General studies before deciding what we would do with IRB's. We may need after getting those results to come up with a fairly significant study of our own, another contract study or something. I am not sure. We will just need to way and see. Furthermore, we have the strong interest on the part of independent IRB's in presenting to us and we have at least a couple of proposals this time that we indicated to you and we would love to hear from at a later point.

So it seems to me that this is something that will come some time after the first of the year when we have some sense of where we stand in terms of available data.

Children and adolescents, an area we have talked about and we need to turn to after the first of the year.

Those are just some of the things on the horizon. Enough to keep us busy for the foreseeable future. But a couple of those, OPRR will have those first two papers by the end of October. And I hope we can get a third one as well.

International, it would be possible I think to do something at the next meeting as well as to discuss at least vulnerability.

Those are some of the things that we have talked about and agreed on as important and said let's do as we can do.

MS. CHARO: Question on the international for October. I want to understand better the purpose of that discussion. I mean I do not discount the importance of a topic at all but I want to

understand whether the purpose is for us to become informed or if it is aimed at making a decision about whether to take on formally as a task a review of the U.S. national policy about transnational research and the adequacy thereof, which is I think an peculiarly appropriate thing for a national commission but I want to understand the purpose of the October meeting.

DR. CHILDRESS: Maybe someone can -- since I do not have the transcripts committed to memory maybe someone can tell me exactly -- Alex, maybe you can -- exactly what our agreement was at the last meeting in July, the one that you missed, and I am not sure I can state it other than that we were going to at least take another step in this area. I am not sure that we committed ourselves to -- I am not sure we have really formulated exactly how far we will go. Is that correct?

DR. SHAPIRO: I think that is right. Do you want me to look at the transcript?

DR. CHILDRESS: Oh, you have it there. Good.

DR. SHAPIRO: I think my recollection of it, and it would be a good idea to look at it, I do not trust my recollection, but my recollection was that we had limited ourselves at that time to saying, well, we would at least address or bring the issue or get a response from the other side of this issue. Mr. Wolfe was here and had presented a set of his concerns and we have since seen a number of documents from that side. And we said, "Well, we would at least want to hear from the other side of this." In some sense we have heard from it. If you -- we did distribute a letter from Donna Shalala which set out the HHS's view of this and accompanied by that paper by Harold Varmus and his colleague.

MS. CHARO: David Satcher.

DR. SHAPIRO: Satcher from the CDC at that time at least. I do not know whether that satisfies it. I would have to go back and look at it but I believe we had took a rather restricted -- at that moment we took a -- we only -- we did not promise a lot.

DR. CHILDRESS: That is right. I agree.

DR. SHAPIRO: That is my recollection.

MR. CAPRON: I think that sounds right to me.

DR. CHILDRESS: But it is obviously one -- not that we have to respond to everything as it becomes a hot topic, on the other hand when there is something this important that is being discussed so widely it is sort of odd in a way for us to be on the sideline completely on it as the National Bioethics Advisory Commission.

So I guess that would be the thought I would throw out but let's see what we want to do and whether we want to build that in. We are going to come back to proceeding with the decisionally impaired research subjects but while we are on this we might as well since this is part of the business we need to conduct today anyhow.

DR. BRITO: Jim, the specific topics of the OPRR, can you elaborate on that a little bit? What would their --

DR. CHILDRESS: Alex, as I recall, had raised this as a topic and you should have also received some material this week faxed -- right, it is probably in this material somewhere -- that carries forward the discussion. But the issue is really whether OPRR is in a difficult position in its current location and whether it should be put in a different place in a department or agency, and so that they really -- it has to do with that. How could it best fulfill appropriate mandates?

Is that fair, Alex? Do you want to say more?

MR. CAPRON: No, I think that is fair. I think we certainly heard from some people today that they have trouble getting the kind of timely review by OPRR because of limitations on the resources that are available to OPRR to carry that out. Whether that would be different if it were an independent agency is one of the issues I guess we will be examining in that pro/con thing you described.

DR. BRITO: I think one of the important issues that we should -- or recommendations or guidelines we should come up with is something Alex mentioned earlier, that implementation of the current rule, you know, like he said the rules from 1977 are not implemented, so whatever we recommend how are we going to ensure that that does get regulated, et cetera, and that is implemented later? So I think that is an issue we need to tackle. This may have to do with the OPRR issue.

DR. CHILDRESS: But he was doing it in relation to the decisionally impaired or --

(Simultaneous discussion.)

DR. CHILDRESS: The reason that those were never accepted and it is the history of this we feel in part with that kind of debate as to how the issues were set up, what kinds of problems emerged, why those guidelines were not adopted, why it is important to return to that area now, et cetera.

DR. SHAPIRO: One small observation. I think that we are going to get some insight into that issue and how we might want to approach it or could approach it when we look at the implementation of the Common Rule which is the next thing we are going to do and what has happened with that. That is also a set of recommendations that came in '79 or '81 and adopted in '91, and we will see what has happened since '91 when Bill tells us. But I think that will give us some insight as to what kinds of things seem to work and which kinds of things just seem to grind on and not really lead to anything.

DR. CHILDRESS: Okay. Alex?

MR. CAPRON: I am sorry. It goes to the decisionally impaired.

DR. CHILDRESS: Okay. I do not know, while we are at it, what would you like to -- in the October meeting, which is definite, right, we are definitely going to meet on October the 19th, that is set. As a subcommittee, decisionally impaired, we

will see what else we have a month from now and talk about. The federal agency report will be further along. We will need to look at that. Those are two things.

Again I will check, I am not sure we will have the OPRR first two papers by then but it will be close. So one -- IRB will be later, children and adolescents will be later. We have Celia Fischer's paper on vulnerability and we will have some other things to talk about there.

One question then would be if we do not have the OPRR papers whether we want to do something in the international research area. That seems to me to be a question that we need to think about and decide. That is at least to discuss the basis even if we do not get someone to present a discussion on the basis of the material that is currently available including what appeared today in the New England Journal.

MR. CAPRON: I think it would be very helpful for people, particularly who were not on the subcommittee but even for those of us who have been trying to follow the outline you just put forward, if after this meeting we could get that outline with the kinds of indications of which report the topic is likely to end up with, what kind of dates we are aiming for.

DR. CHILDRESS: Right. To have the material at least to talk about it seriously like IRB's.

MR. CAPRON: Right. One will discuss the topic and the other, that topic is likely to end up in report number 1, 2, 3, 4. I mean, you know, somewhere because we will have different poles in the air for different lengths of time for some of these things.

DR. CHILDRESS: Right. Fine. Why not try a draft of that subject to our review --

MR. CAPRON: Right. The people who are not here with us on the commission will be helped in their ability to understand what this group is going to be coming up with. It should not be a surprise to anybody.

DR. CHILDRESS: That is fine. The only two things that are in place pretty firmly are the two we are talking about this afternoon.

MS. CHARO: I am very supportive of the idea of taking up the issue of the international research, the transnational research. My personal experience on IRB's has been that the current rules and guidelines that have been issued are insufficient to give IRB's clear direction on specific protocols and I have been a party to debates that have raged for months around specific protocols because of genuine disagreements about the ethics of relative risk in different settings.

I also think that it is really -- of all the kinds of things that are really not best done at the level of academic discourse in journals something like this is right on top of my list because so much of it also involves concerns about intergovernmental relations and we are uniquely positioned to get the voluntary

cooperation of people who work in other countries for the U.S. government to talk about their constraints and their needs and their experiences in a way that they are not going to with the random academic who sends a letter and says, "Help me understand empirically what is going on."

But I would like to suggest if we take it up that we take it up seriously and not just dabble, which I think would waste all of our time. And it may mean that something has to give realistically. I mean children and adolescents is a serious topic. The FDA has put it up on its list again or President Clinton has at least in terms of emphasizing the need for pediatric research. But it is also a topic that has gotten tons of attention and there is a huge wealth of literature. You know, something has got to yield if we add international where it is impossible to focus.

DR. CHILDRESS: Or depending on the time frame.

MS. CHARO: Right.

DR. CHILDRESS: And the children and adolescents we said we would not know about until after the first of the year but we have not said anything more about that.

MS. CHARO: The first of the year is 90 days away. I hate that phrase "90 days."

DR. CHILDRESS: A lapse in memory.

Okay. What do you think? What do you want to do?

DR. CASSELL: I just want to make a timing -- we are about to come out with a report about impaired subjects and it may very well be that we are going to come out with recommendations of things that the IRB has to do and yet we have not really -- we have not looked at them enough to say, "Well, if we are going to ask them more things what things are we going to ask them to do less of," and so forth.

You know, in other words it fits into almost everything we are going to do so that it is --

DR. CHILDRESS: And it is a bit of a chicken and egg problem here. I agree. But it seems to me that there are certain kinds of recommendations that we may be able to make about -- with appropriate sort of protection for populations for such those who are decisionally impaired or revision of the guidance for protecting children in particular that -- I mean there are different levels and, you know, one level is really the common rule. A second level is the set of traditions of interpretations of the common rule by IRB's, investigators and others. And a third is really that sort of mechanism of implementation.

DR. CASSELL: Well, again we have talked today of several people very persuasively about the fact that oversight of a project should not stop once it has been approved and then it goes off into -- if we are going to ask the IRB's to revisit researching process and progress that is a real load, although I think it is very important. It is a real burden on the IRB's and we would be making a suggestion to them where we -- as though we had not

knowledge of --

DR. CHILDRESS: Sure. If we were to come to that kind of suggestion obviously, right.

MS. CHARO: Connected to this by the way, omitted in the kind of list of things that we ought to have happening here at the meetings is one that I think might be important and that is just as today we had a lot of people coming in from the research subject community I think we need to have a lot of people come in from the researcher community and get some more direct feedback from researchers about the experience of working under the regs and under the IRB's. Otherwise we risk always looking at what needs to be done more and omitting opportunities for improvement from the researcher's point of view and I would not want us to become lopsided.

DR. CHILDRESS: Right.

MS. CHARO: But that probably would take some deliberate invited to make sure it happens.

DR. CHILDRESS: And we did a little bit of that at the meeting you missed in July but in relation to --

MS. CHARO: I missed a big meeting.

DR. CHILDRESS: You missed a big meeting.

MS. CHARO: I read the transcript and I still seem to have missed the meeting.

DR. CASSELL: The real -- you could not --

DR. CHILDRESS: We did talk to researchers who are currently dealing with the protection of decisionally impaired subjects.

MS. CHARO: That is true, you did but I mean --

DR. CHILDRESS: So that is not complete.

(Simultaneous discussion.)

MS. CHARO: -- we can talk about the substance of what ought to be done with decisional impairments, but I really mean researchers generically and the experience of doing research under the rules that exist now.

DR. CHILDRESS: Researchers and -- we will get more from the studies that are going on about IRB's, but researchers.

MS. CHARO: You have to understand the one time I went to an IRB I threatened to shoot the chair so I mean --

(Simultaneous discussion.)

MS. CHARO: -- that point of view --

DR. CHILDRESS: And you were involuntarily committed and researchers were not --

DR. SCOTT-JONES: I agree with Alta that it would be good to have researchers speak to us more and I want to remind us that we have a very nice case book from Celia Fischer with, I guess, Kimberly Holwood (?) and Peter Jensen where they actually did interview NIMH researchers and ask them about what problems they faced and how they resolved them. I think that is really a very useful book.

DR. CHILDRESS: As a resource.

DR. SCOTT-JONES: Yes. A very useful resource.

Jim, I do not know if you are wanting us to tell you which of the topics you have listed we think are the ones we should pursue first or most expediously.

DR. CHILDRESS: I am not sure we actually want to do that right now as much as sort of deciding if we are -- given the two things that we need to do at the next meeting whether we want to pursue anything at all at the next meeting on the international. I do not think the OPRR will be very good. We think we could spend some time talking about Celia Fischer's paper on vulnerability. It is really question sort of -- and then I was going to send out a list of the sort of things that we are already committed to, what might be --

(Simultaneous discussion.)

DR. CHILDRESS: -- and then proceed from that. So I am not sure at this point. I tell you I think it would be better to sort of do that and then think about the longterm agenda if that is agreeable with people.

DR. CASSELL: We have two items on the agenda for the October 19th meeting so far.

DR. CHILDRESS: Two things that we need to -- decisional impaired and federal agency report. Federal agency report will have priority because of it being further along and we need to really put it -- move forward to completion as much as possible.

DR. CASSELL: So if we did the international we would really have the time to just begin to touch it?

DR. CHILDRESS: And also I am not sure whether that meeting is -- Harold, I do not know what the conception is at this point, however, but we would hope to build in two subcommittees, and come back as a whole.

DR. SHAPIRO: I think in October it will be primarily the subcommittees continuing to work because I do not think they will be ready very much to focus on recommendations to all of NBAC. So I think -- now we have only one day. We had sort of a day-and-a-half this time and it was easier to arrange so the overlap was two hours or so between ourselves and the Genetic Subcommittee. That will be harder to arrange and I think we can only get one day in which we can get a sufficient number of commissioners here.

So that I look at it as primarily a subcommittee day looking towards either November or December and we have still got some logistics to work out there where the subcommittees can report to NBAC as a whole just where they are going and what the materials are and by that time they will have a substantial number of materials.

MR. CAPRON: Jim?

DR. CHILDRESS: Yes.

MR. CAPRON: Margaret Quinlan has just reminded me that I am overdue to get to my cab so if I could just say two things.

DR. CHILDRESS: Please. I am sorry. I did not know you were leaving, Alex.

MR. CAPRON: Okay.

The first is I think we are going to need most of that day for the federal report. I mean if we are going to do a good job on it.

The second is I broke out the topics that we talked about this morning and the topics that are in Jonathan's paper into seven categories. Let me just very quickly suggest those to you and a few comments. It seemed to me that under that heading of impaired persons we had a basic question about the role of informed voluntary consent from people -- from a person who is capable of consenting.

The question is how -- is that an absolute rule? That is point number one. Should you be able to conduct research with people who are impaired? Should you be able to conduct research with people who are incapable of giving such consent? Should people who can consent now be able to consent into the future? That is topics 1, 2, 5 and 7.

Then there are questions about surrogate decision making. Topics 3, 4 and 6 fit into that category.

There is one thing here and there was a good deal more discussed this morning about categories of research. Excuse me, there are two things. Topics 8 and 13, should research involving decisionally impaired or incapacitated be limited to that which is relevant to their medical condition and should placebo arms ever be prohibited? Those are examples of topics that are here and we heard a good deal more about the therapeutic/nontherapeutic the way that Diane was pursuing that. That would also be the categories of research. I am trying to group these so we have fewer overall topics.

Then there is questions about the categories of subjects. What do we mean, incapacitated? What do we mean, impaired? And there is also questions like the point number 9 here, how are people who are going to be put in such a category notified if that becomes the trigger for losing their right to make their own decisions? Do we think it ought to be a part of the regulations to say the process that you have to go through?

A fifth categorization is specific protections in the research design. Jonathan has mentioned under points 10, 11 and 12 some of those. Consent auditors, reconsent, wrap around studies are examples. Specific protections in research design.

Finally, his 14th point, which seems to me is a separate category, what kind of a role should we have? Should we say that basically the federal regulations are appropriate and what is needed is specific guidance, extra help for IRB's and researchers or are there reasons to have special regulations in this area? I am sure other people will have other categories but I do think it is possible to take what we heard this morning and what Jonathan has in his very useful paper and begin to group the topics so that we can

address them more --

DR. CHILDRESS: Would you mail those to us?

MR. CAPRON: Would I what?

DR. CHILDRESS: Send those e-mail to us when you get back?

MR. CAPRON: Sure.

DR. CHILDRESS: Are you leaving for good? Will you be here tomorrow?

MR. CAPRON: I am leaving for this meeting. Whether I leave for good or not has to do with many other things.

DR. SHAPIRO: We will discuss that in a few months.

MR. CAPRON: Yes, right.

DR. CHILDRESS: I am sorry you are not here for the federal agency report.

MR. CAPRON: I am sorry too.

DR. CHILDRESS: Have you conveyed anything to --

MR. CAPRON: I will send them the marked up draft.

DR. CHILDRESS: Okay. Good, if you would. Thank you, Alex.

Okay. Any last points about decisionally impaired subjects? This grouping, I think, is a very useful one. You might quarrel with this or that and offer alternatives but I think it is a very good starting point. But anything else you want to say about that before we turn to the federal agency report?

DR. SHAPIRO: Jim, I would just say that I think you are going to have a very full day in October with Bill's continuing work and whatever further work we will have at that time on the decisionally impaired issues. It is hard to imagine getting much of any other topic squeezed in, important as it may be for some future meeting.

DR. CASSELL: I would like to spend more time on it, too. I would like us to have a real dialogue by talking. We will have enough by then from what has gone back and forth that we can get into saying, well, this is what I really think I would like to see happening. We can at least start back and forth about it.

DR. CHILDRESS: Arturo?

DR. BRITO: Nothing.

DR. CHILDRESS: Okay. All right. That we will do.

Anything else on decisionally impaired?

MS. CHARO: Did you want to fight through in discussion to any kind of consensus on any of these topics?

DR. CHILDRESS: I think not today. That is my sense unless people would feel strongly that there is one they would like to push. I think the kind of -- I am sorry.

DR. BRITO: Via e-mail.

DR. CHILDRESS: Get Alex's organization structure and see whether we like that and then move into the particulars and see how far we can go with a view that we will talk with John about getting contract help as needed to move forward from this point.

Alta?

MS. CHARO: Well, there are topics. I feel like I will not feel like we are making progress until we start making decisions and as long as we keep planning to make decisions I feel like our wheels are spinning. But I can see the sense in what you are doing and I am not going to fight you on this.

DR. CHILDRESS: I do not feel -- at this point I am so weary I do not feel like fighting.

DR. SHAPIRO: You better move on in that case.

DR. CHILDRESS: I do want to spend the time on the federal agency report. What do you think?

All right. If Alta is ready to fight by e-mail when we are rested then okay.

Okay. Anything else on decisionally impaired?

Okay. Thanks, Jonathan.

Okay. We are deeply indebted to Bill Freeman and Emily Feinstein, and Joel Mangel, and Susan Katz has also joined particularly in writing chapter 1. I think John Moreno joined in a few interviews. So we are indebted to all these people for their splendid work on getting this report in its current form.

So, Bill, let me to turn it over to you to raise what you think are important for us to consider at this juncture.

REPORT ON SURVEY OF FEDERAL AGENCIES

DR. FREEMAN: I would just like to introduce some people so you know what we are doing and who is doing it, and then I think maybe, unless you want us to make a summary, Jim, maybe just open it up for questions. If at that time or later a summary you would like we will do that.

DR. CHILDRESS: One thing that might be useful after you finish introducing people would be to indicate what you take to be the most problematic parts about what you are doing so far and the areas which you think would be most useful to have as items.

DR. FREEMAN: Okay. So that will be good. First of all I want to notice Emily Feinstein, to my left, who has been doing much of the Phase 1 -- actually all of the Phase 1 survey. Joel Mangel has not been able to be here due to a family emergency, which is resolved, but that is why he is not here.

To my right is Randy Hull.

You have in your packet, you received a second packet, the National Bioethics Advisory Commission Human Subjects Subcommittee Informal Feedback by the Regulatees. There was some discussion about researchers and how they see things. This was modeled, as you remember it was mentioned in March, the suggestion actually came from you folks to do this, because we are modeling after what happened what you all did in cloning which is to send out an open invitation.

We sent out three letters to three groups to researchers in the federal -- federal researchers who are being regulated by the federal IRB's and then secondly IRB's with multiple project

assurances regulated by OPRR, and IRB's by single project assurances. There are about 3,000 of those and almost a 1,000 of the MPA's.

We are just getting stuff and if you have any questions Randy -- this is his report and he can help discuss about that.

Finally, Susan Katz is our editor, our writer, our alter ego and all that good stuff for the report that you have.

I apologize, by the way, for the first draft that did not have pages. That is why you have a part of that pile has not been close to being too much. Today was the draft chapter 1 and 2, just pages so it is easy to look at the pile and to refer to, and additional -- for those who have read the earlier draft you do not have to read the one with the pages except for the very last two paragraphs on Category 4 on page -- what is now page 14 -- and the last sentence of Category 2 in Chapter 2 was an addition. That was the one about an additional chapter or an additional sentence, excuse me, about agencies that have problems of wide dispersal of their IRB's, their larger organization and a system to monitor the quality of the IRB's.

As a summary, since Jim was asking -- I was actually hoping that you all would ask me questions first -- but I summarize -- and I think this is the sense of us here. We have been talking about this a great deal. I am going to give two-thirds of a sandwich. You know, the old sandwich. A nice thing about -- it is going to be two-thirds.

The nice thing is that there are organizations in the federal government that are doing extraordinarily well not just complying with the federal regulations. They have solved -- they are confronting problems and have imagined its solutions to those problems. By memory that is Category 2 in the report. There is -- it turns out when you look at Chapter 1 which gives the history of all the previous surveys, some of that is apparent in those agencies as well in those reports.

And I am impressed being an IRB chair myself in the Indian Health Service, one of the federal agencies, of how much I have learned personally from these things that other people are doing. One of the things I found is that I did not know about it and no one else knows about it, and the federal government is self isolated. Parts of it do not speak, you know, one part does not speak to the other. And so we are confronting problems that some other part of the federal government has solved and we do not know it. Actually perhaps a recommendation might be some sort of effective sharing mechanism.

That is the first third of the sandwich of the two-third sandwich, and the second half of the two-third sandwich is there are some federal agencies whose performance since 1991 or before was unacceptable. That is a term that in discussion with some of the people here last night seemed to be about the right strength and convey what we have found. That is Category 4.

Within that group, as I said, there in the draft or as we said in the draft there are some people who were truly ignorant and just did not know about it. It had not gotten to them about the need for protection of human subjects in research and that there is regulations about it. And when they heard about it at our interviews they have started to do steps. I hope they will be effective steps but nevertheless they really supported that they are doing steps to come into compliance. It is not just compliance with regulations. It is, indeed, to protect human subjects.

There are others that we did not get that impression at all. They did not report since our interviews that they have really either agree with it or that it is a priority. That is the basis -- that is the report I think in a nutshell.

MS. CHARO: Bill, I still do not -- I really appreciate all the detail and a lot of what you documented here actually has to do with the process of gathering information and the obstacles there which makes it easier. But I am still having trouble grasping the kind of draft bottom line of the results. There are some agencies, number unspecified, that have failed to implement the Common Rule in a way that actually protects human subjects, right?

DR. FREEMAN: That have failed to implement the Common Rule at all.

MS. CHARO: Okay. Any clue as to whether these are agencies that have large or small research programs? Is this a big problem or a little problem? Is the research they do the kind of thing that gives people just a physical injury or is it psychosocial stuff that varies tremendously from serious to trivial so I can get a sense of how alarmed I ought to be?

DR. FREEMAN: I think that is a very good question. There are two categories. Many of the agencies that were unaware or thought the regulations did not apply them tend to have small research portfolios either that they do themselves or that they fund and sponsor. They tend to be low risk, from what we can gather, low risk research.

There really -- I should have mentioned there were some that were totally ignorant who really did not know and others thought that it did not apply to them because they were "exempt" in this group of low number of research projects done or supported.

As far as we can tell, but we have not looked at the protocols, as far as we can tell both the numbers and the risk is low and one of the reasons that at least those who thought it did not apply to them, that may be -- it is probably misjudgment -- was because of the perceived burden, at least this is our impression, of the regulations.

There was a -- at a meeting that Jim, Emily and I and others were at Friday, the description was it seems like if you have a single research project that is over the line and no longer exempt you have to deal with an 800 pound gorilla worth of procedures and regulations and activities that you have to do to deal with it, and

can it be made into for a low volume -- an organization that has low volume of research can be made into a 20 pound lap dog kind of thing.

There are other organizations that do a lot of research or pay for a lot of research, or both, with vulnerable subjects and whose practices -- whose, as far as I can tell from reading descriptions of the research, does get into the greater than minimal risk category. It is for a high volume of research.

This -- NBAC has been looking at a very important vulnerable population, the cognitively impaired. As you saw in something I sent out, which on rereading I wish it was more understandable, but it is possible of what policy and ethical issues and exempt research implications from our survey.

MS. CHARO: Right.

DR. FREEMAN: I am not sure that the cognitively impaired are the most vulnerable at this time in the United States. I think people in the criminal justice system and people near them, which is to say near the criminal justice system, their family members, or people who live in high crime neighborhoods may be at significant risk for research that has not been adequately assessed.

DR. CASSELL: Could you be more specific in the examples so we understand a little better?

DR. FREEMAN: If you are doing research of surveys on crime victims in a high crime neighborhood there is a risk of retaliation simply by being interviewed. To my knowledge there is that kind of survey going on. That is not to my knowledge. There is that kind of survey going on. To my knowledge I do not know how adequately that kind of risk has been assessed and minimized.

MS. CHARO: Do you know if it has ever been realized? Has there ever been retaliation?

DR. FREEMAN: That is what I -- let me --

DR. CHILDRESS: Assessed minimized but also disclosed and explained.

DR. FREEMAN: As well as disclosed and explained. I do not know if there are examples of people who have been physically retaliated against. I do know that in -- many of us who have as IRB's looked at or researchers who have looked at especially research on domestic violence, victims of domestic violence, that is a major concern of me when I review it and it is not -- I bring up with researchers if they have not thought about it -- when it is brought up to them they do not disagree that that is a significant risk. I do not know if anyone has been physically harmed, however, by the lack of attention to that or even not lack of attention but just by the research but it is certainly a potential risk.

There are risks of -- in the current system, and we should separate out whether it is compliance with the Common Rule and what should the policy be about protection of human subjects, and it is more than the Common Rule. It includes those other

statutes and codifications of statutes that are supposed to protect human subjects.

In that system it appears that if people are interviewed and they give information that may say something about their future criminal behavior that is not protective as confidential even though the research is being carried out under the exemption of the data will be confidential. By the way I am not saying that it is appropriate to disregard information about future criminal behavior but one of the -- in research that I have reviewed and that is fairly common in the survey research in Health and Human Services, child abuse, the best predictor of future child abuse is current child abuse or past child abuse with the same situation.

We deal with that problem about the potential about being informed of something in the future or for that matter in the current all the time. That to my knowledge has not been addressed and so you may have people in the criminal justice system are not always the most functional people around. They may disclose their future criminal behavior in a setting which they do not understand that that can get them in trouble.

MS. CHARO: Bill, I am intrigued by this and I was intrigued by your memo but before moving along on that, which in some ways is speculative because there is no data, I want to come back to the findings from your survey so far if I can.

DR. FREEMAN: Okay.

MS. CHARO: If I understand it correctly, by and large what you are finding so far is that the very same agencies that do fairly little research with human subjects that has more than minimal risk, it is those agencies that by and large are the ones where you are finding lack of implementation or inadequate implementation of the common law. And yet if I think back to the agencies that have been hit with scandals over the years, I think about the Department of Energy, the Department of Defense, the Veterans Administration, and NIH itself, all of which are agencies that presumably are not in this category of places that have failed to implement the Common Rule.

So I am trying to figure out based upon what you are finding how to explain that the agencies that appear to be implementing the Common Rule are also the ones that are having all the scandals. Now it could just be statistical. They are doing most of the research and that is where most of the scandals are going to be. But maybe it is something else and I want to try to get a handle on it because I know that the point of this exercise is to figure out where the federal government needs to improve to actually make a dent in preventing the scandals from arising again.

MS. KATZ: Can I just clarify something in terms of my understanding of the report. I was running fairly late in terms of writing it and was not in on much of the design of the study to begin with. But you should understand that particularly Chapter 2 which is an analysis and discussion of the data is in very

preliminary form.

MS. CHARO: Sure.

MS. KATZ: That basically we are still getting edited responses from the agency. I think that some of -- and it was, you know, I think quite properly rushed out so that you could have something to discuss today. But I think that there is some danger in trying to draw the kinds of conclusions that you properly are trying to draw on the basis of the analysis that has taken place thus far.

That is what you have been presented with at this point and what we have focused on up to this point although we may have speculations about what the data will show really focuses on the structures that have been put in place for implementation, that is, you know, can you say that an agency that has put no structures in place, you know, you clearly know that there is not going to be an implementation there.

On the other hand agencies, and I think this is what you are getting at, which have very -- you know, ostensibly very, very complete structures in place there may also not be true implementation or true protection. I am not sure that -- you know, although again we can speculation in some senses in terms of the draft in the report, I am not sure that we can make those kinds of assessments at this point, you know.

MS. CHARO: Your point is well taken and --

MS. KATZ: I really think that they should be data driven.

MS. CHARO: Yes. I regret kind of demanding an answer before you can give it. But there is a kind of phenomenon here. I mean you can say based on preliminary data that interestingly enough the places where we find the worst implementation at the level of having formal procedures, formal officers, and formal designation, is not the same place where we seem to be finding most of the scandals. So it would not appear at this early point that a lack of offices designated efficient, et cetera, is going to be the explanation for the scandals we have had.

So our preliminary results so far is that we are going to have to look at something else, that whatever it is we continue to do it is going to have to get at something besides formality. So that is not to say that formalities are not important to document. We will have to finish this up and complete it for the sake of being able to report it. But that we have yet to identify the kernel of the problem here, you know.

Maybe you are uncomfortable speculating what the kernel may turn out to be but you may be able to speculate about what it is definitely not as you clear things out.

DR. FREEMAN: I would be surprised if we will be able to speculate well even after the report about what you are really after. Phase I is structure. Phase II is process of those who have a structure in place. And we will be able -- and there it is still

a three-hour interview and very detailed understand. But it is limited just on the nature of the beast of what we are able to do. I think we will be able to detect, we already have, some problems in Phase II. But I am not sure we are going to be able to say here are characteristics of an organization that is ripe for scandal and be able to predict that.

As a matter of fact what you are going to find is just the opposite. Scandal -- if you look at the agencies that have scandals in the past and what their structures are now, and some of it is in the report, that is a Category III, I believe, of people who have been improving recently in the past 12 months is how we define it. And some who have been doing that for longer have been responding to scandals.

So, in fact, what you tend to have in association of -- right now in our cross-sectional view people who are doing very well being the ones who have had scandal in the past. But, of course, the causation is that the scandal caused them. They responded to the scandal.

I do not know if we will be able to identify factors that are -- will identify an organization being set up for the next scandal. It is possible but as Susan said we are looking at structure and process. About all we can do, I think, at this point is to say with Phase I there is a structure in place or there is not and a little bit more. Again we end up with four categories and we define those categories that way.

And with Phase II we will be able to talk about process and some processes that seem to be good and evidence of processes where there is limits, whether they are up against the limits of the regulations or they are up against the limits of the implementation, the current implementation of regulation.

DR. CHILDRESS: Diane?

Alta, were you done at this point?

MS. CHARO: Yes, the inquisitional stuff for the moment.

DR. CHILDRESS: Diane?

DR. SCOTT-JONES: I would just like to clarify what you have done so far. You have completed all of Phase I and all of Phase II, is that right?

DR. FREEMAN: No, we have not completed all of Phase I but we are very close to completing all of Phase I. We wrote Chapter 2 which is the description of that and I will be honest at this point, as Susan points out, it is still a draft. On the assumption that with the remaining ones which tend to be low volume organizations that do a low volume of research if they do research, that we are not going to find any new patterns. We will find information about that organization that we have not done and there will be a table about that organization. But we are assuming that by and large we have found the patterns and so we can come up with a draft as we are completing the research.

Phase II we do not have a draft yet because we do not have enough of the Phase II -- we have not done enough interviews of the Phase II organizations to be sure about -- reasonably sure. We have come up with -- and we are discussing it because it is too preliminary as I just said minute ago -- patterns of process that could be improved or weak patterns of limits. People who have come up against the limits of the current regulations or people who have come up against the limits of the implementation, the current understanding of the implementation of the regulations.

DR. SCOTT-JONES: So are you expecting then that some of the comments that you made in the document that we now have might be changed once you get the Phase II completed and summarized? That is some of the things, for example, at one point you mentioned that something raised more questions than it answered or something like that. I was wondering if you are expecting that when you get that you will be able to say more definitive -- make more definitive statements.

DR. FREEMAN: I think there are two questions and I will take the second one that you have just asked and deal with it first. I think that was in Chapter 1. Those were the responses to the Executive Order as well as the findings of the previous commissions in their surveys that we found that to try to get a full understanding of the federal government. There were, as I said -- as was said, questions raised at -- or answers that raised more questions.

One of the things we found out of that by the way and we are finding in our survey is that when one concentrates at the department level for the response, be it by a commission or letter from the President as part of the Executive Order, that covers a wide variety of behaviors by the different agencies within the departments. We really need to go at least the one level below the department level usually called an agency to understand what is going on in that department.

DR. SCOTT-JONES: And we have not done that?

DR. FREEMAN: That is what we are doing in Phase I. That came from the replies to the President's Executive Order and from some of the previous surveys that have been done. HHS was divided down into agencies although not all the agencies were interviewed or surveyed. Many of the other departments were done at the departmental level. And we are finding that when we go to the agency level that we get this marked variation between agencies.

MS. KATZ: Can I clarify one thing as well? I think part of the confusion is that although the face-to-face interviews, in-depth interviews that the agencies have called Phase I, it was not really Phase I of the inquiry. Phase I of the inquiry which is reflected in the introduction were the responses to the Executive Order from the agencies, the written responses.

DR. SCOTT-JONES: Right.

MS. KATZ: So that there was sort of a base

investigation of those responses which the problems with which are detailed in the first chapter, which led, you know, Bill and Emily and Joel to go on with Phase I study. It may be too confusing actually to call that a Phase I because, in fact, Phase I of the inquiry was the review of the agency responses. So I think that is where the confusion is.

DR. CHILDRESS: I think that is a good point and it might help. We have to be careful about that in the presentation in the final report.

DR. FREEMAN: There is also a difference between Phase I that is in Chapter 2 versus Chapter --

DR. CHILDRESS: Right.

DR. FREEMAN: We will -- a good point.

DR. CHILDRESS: I think that will help clarify it because these reports actually existed before NBAC came into being but they were mandated as reports that had to be provided within 90 days as I recall and they would go to NBAC and then they came to us when we were created and now we are going to have to look at them. So that is -- the question you were raising really addressed that set of concerns relative to the earlier commission's work.

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DR. FREEMAN: Right. However, the other question you raised, which is are what we have written in Chapter 2, is that possibly going to be changed by our future work? Is a term divided into two things. I think Chapter 2 in whatever phase it is you want to call it of -- that is looking at structure probably will stand relatively alone.

Our second phase, I do not know what you want -- the set of interviews where we are going to look at process with people who have structure -- organizations that have the structure in place and looking -- interviewing people like the chairs of the IRB's. That will be a separate chapter and I am assuming it will stand alone. But it is possible that results from there may feed back and change what is your draft, our draft, of Chapter 2.

It is also possible, always possible, that we will find something new in the remaining interviews with the structure phase. Maybe we might label them structure phase and process phase. The first set of interviews was around structure.

And so this draft, first of all, is not completed about Chapter 2 and, yes, it is possible that it will be changed although we have no evidence to think that that will be the case.

We have got about 40 interviews?

DR. FEINSTEIN: More than 50.

DR. FREEMAN: More than 50. So I think that that is -- and we intentionally did the ones with a high volume or we thought were risky, or whatever, early so that the remaining ones we think will not be -- give us a new pattern.

MS. KATZ: What will change is, hopefully, there will be some information that will address the kinds of concerns Alta was raising, which is, you know, at a closer look at the data that we already have. Do patterns emerge in terms of the agencies difficulty in implementing and why? You know, that may or may not emerge but it is certainly hoped.

MS. CHARO: From what you have seen in that data is there anything coming out of that intramural versus intramural research?

DR. FREEMAN: In what way?

MS. CHARO: One of the things that is often cited as a problem with IRB's is the inherent conflict of interest of having peers interview -- I am sorry -- monitoring one another. Well, on the federal level intramural research represents that problem whereas intramural research does not. I am wondering if in the most preliminary fashion you are finding any distinct differences in the course of your interviews in the comfort level or effectiveness of the intramural research program with its own internal review versus the extramural program.

DR. FREEMAN: We have not looked at the extramural program yet and we could only look at the people who -- the process to, you know, approve grants and OPRR's review of that and other

departments review of those. So I do not think it is going to be quite comparable as at a university. But conflict of interest and tension around influence of peers to the IRB, to the intramural IRB, intramural peers to the intramural IRB, we do ask a great deal about and there is variation.

Preliminarily it appears that especially when the superiors in the organization make it clear -- and Dr. Moreno can maybe because he has been participating in some of these come up to the mike and give your input if you would like -- but when the superiors in the organization make it clear that they value the protection of human subjects, and that comes first, it is a lot easier for an IRB to -- IRB members to say, "Okay, we will be independent."

There have been a couple of times where people have expressed discomfort with the situation, that there may be -- it is not just an immediate superior. It may be the PI is a person who approves my member of the IRB budget, for instance. All sorts of possible things. There is at least some discomfort expressed. Although not that that has altered decisions. It is just a discomfort that they have to deal with.

DR. MANGEL: Well, I do not have much to add to that. I think in some cases in some of the interviews that I sat in heads of organizations actually joined the IRB chair for the first part of the interview and that actually proved to be very useful from the point of view of gaining information about how decisions were made in the organization and also was to some extent revealing about the way -- the extent to which there was communication from the top to the IRB chair.

Actually rather than making me feel that the IRB chair is being intimidated it made me feel that the chair felt more able to act independently if that director really was supportive.

DR. CHILDRESS: Other points people would like to raise?

One I would mention that came as part of our meeting last week, on Thursday of last week -- was it Thursday or was it Friday?

DR. FREEMAN: Whatever.

DR. CHILDRESS: Some day last week.

DR. FREEMAN: I had that Maryland fish and I do not know what has happened to my memory.

DR. CHILDRESS: And that is that problems arise in part as experienced by agencies and departments doing research in part because of some of the uncertainty regarding or sense of burden of the Common Rule itself. You have mentioned that burden in passing. But I think it is also important to keep that in mind as we are drafting this that that is something that has been expressed to us and we would want the final report to reflect some of those kinds of concerns that have been expressed by the agencies who have been interviewed both in terms of structuring and the process.

DR. FREEMAN: If you think about what has happened with the implementation -- let me give another sort of summary thing. One lesson that we learned is that regulations -- these regulations are not self-implemented. I think as soon as one says that someone says, "Oh, but of course they do not." But it is not clear that that observation has been in the mind set of the federal government, thinking that the federal government has a system for the past 20 years.

Secondly, there is plenty of research about the process of who implements and how fast, and it is a sigmoid curve. If you have the percentage of people from zero to 100 percent that implement in time it looks like this. It is that last tail which takes a lot of time for the last 10 percent where we may now be at. I do not know if it is 10 percent. I have not looked at the numbers.

But there is some experience about that and usually for that last remaining group of that hump of a sigmoid curve that often additional efforts are required to get them to implement. This is, by the way, research with the Agricultural Extension Agency in the 1930's. That is when it first came out and it has been reverified in other settings. So we may be there. This may be what the problem is about, is that last X percent that just is not doing it. I suspect it is more than that but at least that is one of the factors.

So one of the things that can be done is how do we -- what can we learn from organizational research about implementation and about maximizing the speed and percentage of people that implement. Well, among other things, you minimize the cost of implementing. That is reducing that 800 pound gorilla down to the 20 pound lap dog. Other incentives that may be required and so on.

So that may be some of the things that your perception and experience can be put into the conclusions and recommendations of the report. Some things along that line may be helpful.

MS. CHARO: You know, I am not -- I keep finding myself wondering what to take away from this because the point of forcing implementation is not merely to get everybody in compliance with a rule because it is on the books, it is because you think there is actually a net benefit to that otherwise the correct action is to suggest changing the rules because it is a support for this rule.

And I find myself wondering if we are at risk of slipping into a mind set in which the resulting report is going to be here is what we need to do in order to get the last 10 percent to implement. It may not be a bad idea to get them to implement although it may be more productive to think about scaling back the rule if it is really not needed since there has been no problem and they did not implement it. You have got some minimal concerns about uniformity.

But to make sure you do not miss what the main thrust of what the report is eventually supposed to be the whole impetus for

this thing is that there were scandals and the whole impetus for this investigation was the suspicion that the federal government was doing a bad job at governing itself in the area of research. So if we wind up only with a way to --

DR. CHILDRESS: And a bad job --

MS. CHARO: Right. If we wind up with something that is an accounting job in which we accounted through the federal government for places where implementation is incomplete and where you need to add a DFO or you need to add an FTE we will not have actually answered the substantive charge. This is not aimed as a criticism to you. But it is just kind of a feeling that we might be slipping into that as the kind of conclusions to be drawn from the report. That would be foolish. It would be a missed opportunity.

DR. FREEMAN: It would be and I think I am glad you said it. What we have done is I hope not to slip into that in terms of our work but what we reported today is shorthand. Implement the regs in shorthand for protecting human subjects. We have looked at it and have recognized when an organization may not have implemented the Common Rule as commonly understood but has protections of human subjects there and when it is there not even a structure to any structure, significant structure, to protecting the subject. The same thing with the process, that process phase.

I am hoping that -- and you have reminded us to make sure that our writing reflects that -- that we, ourselves, are very clear that there is a difference between the regulations and the protection of human subjects. They are not the same as simply implementing regulations. It does not mean that one is protecting human subjects and that seems -- that just seems to -- concluding in that memo about the criminal justice thing.

MS. CHARO: With that said, of course, I am also not saying that it would be a good thing to have them not implement because I am not sure that --

DR. FREEMAN: No, I understand.

MS. CHARO: -- we want to encourage that either. I do not know what I want to say at this point.

DR. CHILDRESS: It is something that needs to be carefully thought about in the preparation of the report.

MS. CHARO: Yes.

DR. FREEMAN: And not only carefully thought about but carefully expressed to make sure it says what we mean it to say. In the shorthand that we used in the session today is not helpful.

DR. CHILDRESS: Diane?

MS. KATZ: May I just point out that in the first page of the introduction the two things that you are talking about I expressed in two totally different questions. One is are there institutional structures in place to implement and the last one are the regulations in the structures functioning to provide actual protection?

MS. CHARO: Right.

MS. KATZ: There are really two very separate questions. I think the focus of the data that is in Chapter 2 is probably are the institutional structures in place. Whether or not those structures and whether or not the regulations, you know, themselves when you talk about are there really problems of the Common Rule are functioning in a way to provide actual protection is something that has not been addressed and I absolutely agree that it is a critical issue.

MS. CHARO: Okay.

DR. CHILDRESS: Although just before -- the other side of that, I guess, would be -- this goes back to an earlier question Alta raised about what evidence we had of where -- where the regulations and structures were not even functioning there was actually harm to research subjects or violation of their risk -- of their rights. I mean that --

DR. FREEMAN: Or both.

DR. CHILDRESS: Or both.

DR. FREEMAN: Because they are separate issues.

DR. CHILDRESS: So that seems to me to still be something that does not come through clearly here as well.

MS. CHARO: Philosophers really talk about things being -- a condition being necessary and sufficient or might be necessary. It is clear that the regulations and the implementation are not sufficient. What is interesting is that you are hinting that they may not even be necessary which is a very disturbing conclusion that you could draw from this.

DR. FREEMAN: Nothing you think of -- because you are expressing a perception that some of the agencies that do relatively little research have said. Since most people -- I think Eric's take on it -- since most people want to do right and by and large most of the time they know how to do right, not all this other stuff, when you have an organization that is relying on not careful thought about what are the possible risks to people, research subjects, they can get away with not harming people so far as they know because most of the time research does not harm people. It is the once in a while research that harms people and then even there it is the once in a while of the times that people are harmed that anyone knows about it.

MS. CHARO: That is true.

DR. FREEMAN: And we -- when we sit down and talk -- on our interviews we have talked with people in those organizations and say, "Look, this is your survey. This is the possible risk." They do not say, "Oh, that is okay. It will never happen." They recognize that that is a risk and that they have not had sufficient oversight to minimize that risk. So I do not think anyone even in the organizations that have gotten away with no scandal and have no structure right now would say, "No, we do not need it."

DR. CHILDRESS: Diane, and then Eric.

DR. SCOTT-JONES: Well, actually I think the

conversation has gone all around what I was going to say and we were kind of excluded from it.

DR. CHILDRESS: And now back to it again.

DR. SCOTT-JONES: It was just to point out that what Alta was commenting on is actually on the first page as you have said. The last question does ask if the regulations are functioning actually to protect the rights and welfare of human subjects. So I would assume that at one point or another you will talk about that.

DR. CHILDRESS: Eric?

DR. CASSELL: Well, I think I am just really summarizing what I am saying but one of the purposes of the report is not merely to show we surveyed all this but to say that they do not let people die. I mean one of the things about that that you just talked about in the criminal subjects and so forth is the people who are doing that does not think of it in the terms of the regulations. Those regulations are getting penicillin to one group and not to the other group. It is not about people in a crime ridden neighborhood being asked questions.

It is those conceptions that underlie much of the problems we heard today. You know, fundamentally not understanding what is done. I think when you bring those up and when you highlight them in your report you bring new awareness to people, "Oh, that is what it is about," rather than to just set a regulation. I think that is going to have to be one of goals because we hear again and again of people just not understanding. Not being bad guys but not understanding. I think it is terrible some times but --

DR. CHILDRESS: That point is well taken but it does connect in with the issue of making sure that when we move to the final draft of the report that, you know, we have captured it in language and so forth that will really awaken the consciousness.

DR. FREEMAN: I would just like to add to what you said. The reason I think some people do not understand or have not got it is because the incentives are such that they are against them. One of the -- again one of the incentives is that 800 pound gorilla. If you have an 800 pound gorilla it sure is easy not to understand. If you think that is what it is going to -- what is the implication. And we have done that with -- a couple of times, without naming names, we will be meeting with one of these organizations in the near future and precisely that is what our approach is going to be.

The very first thing we are going to say is, "Look, I think much of the stuff that you are doing or that you are not doing could be done in this very easy way," and see if, in fact, that sort of removes that barrier and they say, "Oh, okay, now I think we can understand some of this research is not exempt and needs to be looked at."

MS. CHARO: Based on what you are finding just in terms of structures, I am finding myself wondering if another thing we can try to draw out of this report would be the beginning of an answer

to some of the questions that Alex was asking, I think, at the last meeting I was reading in the transcript.

Alex was jumping up and down last time as I understand it about the fact that --

DR. CHILDRESS: On the basis of the transcript?

MS. CHARO: I can see him in the transcript jumping up and down about the fact that the President's Commission had been demanding information about the number of research subjects enrolled and in what settings back in the early '80s and that today we still cannot answer those questions.

Now would the data that you are developing that includes information on things like do you have an IRB and with the IRB comes record keeping, you are also incidently answering the question of whether or not you have structures in place that could, in fact, go through the records and answer some of those questions that Alex is asking. It is not going to tell us how to do it across the country but it gets us started at least on the federal government having an account of that kind of data or being able to do things that will give a sampling to get gross estimates of the number of people enrolled in research and of what type and levels of intrusiveness, et cetera.

Do you think it is feasible to begin to draw some conclusions out of this about what it would take for the federal government as a leader to begin to answer some of the demands for information that were worries back in 1982?

DR. FREEMAN: I am not sure we will be able to answer what it will take. My -- we asked some questions that were asked in February on the survey and found that they were not helpful. Like how much money is spent on research and how much money is spent on your IRB. This kind of stuff. Some could give it to us easily and others could not. We decided not -- if they could not give it to us easily -- not to require them to spend a lot of time trying to give us a number that probably, in fact, would be incorrect. It would be something that would be a fictional number. Maybe in the neighborhood but you know how it works when these very difficult questions come down. The reason was we did not want to add to their burden.

I would say one of the things we have found is that a tremendous amount of the federal government is doing a tremendous amount of research and when you think about it you want that to be the case. You do not want the federal government to be doing things, implementing policies and so on without some empirical base.

Is that part of the problem about this remaining X percent?

Then the question is what are you going to keep records on? Is it going to be on everything that is exempt? Currently, for instance, I think NIH can do that because any time there is an exempt -- whether it is just one organization -- any time there is a

possible -- a proposal that is possibly exempt it goes to the central office at NIH and they fill out a form so they can make sure they get enough information and then the central office does an analysis on which they can make a decision.

An IRB that does not do that for that kind of research will not be able to keep the records.

MS. CHARO: Okay. Let me rephrase it. Think about the drama if you were to ask every one of these agencies that you have been interviewing through paper and face-to-face tell us how many people have been enrolled in nonexempt research in the last year and then you found out how many agencies could actually answer that question. I mean, could they actually answer that question?

I mean, that to me is the kind of data that gives us some insight into how realistic it is to be able to get a handle on what it will take to prevent people from ever being enrolled inappropriately. For an agency -- if an agency does not even have the self-realization at the levels of administration as appropriate of the scale of research going on because there is no kind of centralized data we would be in the most minimalistic kind of demographic data that they are unlikely to have a sense of whether or not there is an urgent problem or a nonurgent problem of implementation required by an agency that is self-implementing.

So unless there is some kind of awareness in the administration, "Oh, you know, this is a big part of our portfolio." This really deserves some serious attention. You know it will not happen unless, of course, somehow there was, in fact, a super agency for human subjects that stood above all the secretaries that could force that action but that is not the case right now. So you depend upon the secretaries looking at their agencies and prioritizing tasks.

Somehow -- maybe it is just, you know, very late in the day and I want something to like wake me up but --

DR. CHILDRESS: It is called Coca-Cola.

MS. CHARO: Yes. I feel like that there ought to be a way to get at what is in here to get to stuff that is going to be ever closer to something that has a policy implication.

MS. KATZ: I think that one of the things that I have seen in my very preliminary review of the data that was collected, that struck me in any event, is the continuing problem with the definition of research. You talk about the distinction between therapeutic and nontherapeutic and, you know, the sorts of things -- the sorts of difficulties that were being addressed this morning. You know, you go back to the beginning and try to get people to figure out whether or not the agency is doing research.

Now that is a fairly fundamental problem as I see it. And I was somewhat stunned and I think that can be emphasized. That is still a problem and it is a big problem. If an agency does not understand that they are doing research then even if they have structures in place they are not going to be effective. So, you

know, I think that is something that really needs to be addressed and that is a fairly --

DR. CASSELL: And their research may be no good.

MS. KATZ: Pardon?

DR. CASSELL: And their research may not only be unethical but no good.

DR. FREEMAN: Let me just -- the difficulty is not -- actually we have a structure in place in order to do some research. The question is, is this thing, this activity research or not. It is difficult when you are doing internal program review, internal management, quality assurance, you have got small groups, you are making conclusions, you know, about groups. It is easy to extend that or not. It is difficult sometimes to know the difference. I have trouble knowing the difference because I am involved in quality assurance as well.

That is where some of the problems are going to be. Animal research is -- you know, at least you are dealing with the animals and most organizations, aside from having pets or eating them, it is research. So it is relatively a sharp demarcation. If you are doing -- you know, if you are in an organization that does some research and you have an animal and you are doing something with that, that is research. It is easy to understand.

MS. CHARO: But see now this is actually a very productive line because in the course of your Phase II in looking at process, right, if what can emerge from there is an understanding of the range of confusions that occur over whether what I am doing is research, as well as whether what I am doing is exempt. It is not that I have the structure. I have the regs. I have implemented them. I know that if it is research it goes into this box and if it goes into this box and then if it is called exempt it goes into that box but I do not understand how to apply the regs.

There are conclusions to be drawn there even about education of agencies or about the redrafting of the regs, or about the redrafting of the guidance. That often in terms of examples but there is something very useful to be pulled out from that. I would be delighted the more we can find that these kind of pressure points in there and take advantage of them.

DR. FREEMAN: In the meeting last Wednesday that Jim and I went to we talked about something that I think -- that I believe we will be looking at that. We have preliminarily, and again it is for the guidance of the commission, sort of three major things that the report needs to deal with.

One is what is the direct implication of the report, directly out of the report? That is going to have to be again some of your stuff advising us on that. The second this is, is there anything about the Common Rule and all the other regulations themselves as written? Are there limits to them? They do not deal with communities. They do not deal with third parties being harmed by research. For instance, major things around genetics. So we

already know that there are limits there. These are coming out in our process surveys.

Then there is the issue of how to implement. What is there? That includes how do you -- what are the structures that are required? How to make it understandable, the regulatees.

DR. CHILDRESS: Any last comments? I know a couple have to leave.

DR. FREEMAN: Jim, I have got a question. I had not realized that the October meeting was not going to be a full NBAC meeting and that it would be devoted then to the subcommittees before they make a presentation to the full NBAC. It would appear then that the government survey report will not be finalized -- well, I am asking -- let me ask, are you expecting it to be finalized in October or the December meeting and that at that time all of NBAC signs off on it and then it gets sent to the President? Is that our --

DR. CHILDRESS: I -- sorry. It looks as though if we do not do the November one which comes just prior to the December one anyhow that we will only have the October 19th and then the December 1st. So it looks as though that will be the best that we can do. So I guess the question would be if we can move the report, you know, as pretty close to as final as we can in a month that would be great but we just have to do that to be done.

DR. FREEMAN: It was just so that we --

DR. CHILDRESS: If it cannot be done it cannot be done.

DR. FREEMAN: No, it --

DR. CHILDRESS: We do have a long gap between that 19th of October and December 1.

DR. FREEMAN: Actually, our November meeting is going to be a week before the December meeting or something.

DR. CHILDRESS: Yes. It is not -- as Alex pointed out in the memo there are only three working days between the November meeting and the December meeting which raised questions about whether we should have both of them.

DR. FREEMAN: Actually just to understand that it looks like the -- we would still like to have a draft as much definitive for the October meeting from the staff but there is going to be two steps. The subcommittee will review it and then all of NBAC.

DR. CHILDRESS: Which might occur then at a subsequent meeting but at the same meeting.

DR. FREEMAN: It also can occur obviously as has happened before over e-mail and everything else before that December meeting so that the meeting is just a sign off.

DR. CHILDRESS: Yes.

MS. KATZ: Are you talking about the final report as in recommendations as well prior to the time that the subcommittee really has a chance to consider the data and decide what they want to say?

DR. CHILDRESS: Well, we have to see where we are on the

19th. Now, we have to see where we are on the 19th.

DR. FREEMAN: I am assuming that the recommendations will come out of the 19th meeting.

MS. KATZ: Will come out of the 19th meeting so that they really will not be part of the report at that time.

DR. CHILDRESS: Right. But if there are things that you think we are ready to recommend obviously we would want you to offer the proposals regarding those as well and things have already emerged today about possible directions for recommendations.

Eric?

DR. CASSELL: I want to urge you to have a truly narrative report because you have so much data that the danger is that, you know, only some points of that data that you -- that the generalized points do not get made. So that somebody can pick that up who never even looked at the data and read that and get a sense of what really does happen in this country on research subjects. I mean, I am sure you are going to do that anyway but I urge you.

DR. FREEMAN: That was the goal. Our goal is to have a 50 page narrative and all the other stuff, tables can be in appendices, but a 50 page narrative.

Now let me ask, if I may, the first two chapters, did that accomplish -- that is what we tried to do. The reason I am asking is if we did not do it then we need to know that because that is what we tried to do.

DR. CHILDRESS: One response might be it may be at this point, and I think it came out in comments, a little too compressed.

DR. CASSELL: Yes.

DR. CHILDRESS: In other words to say we may need to sort of open it up a bit so that the important points really become salient. The discussion on research, for example, may need to be unpacked a bit more.

I do not know. Did others -- that would be just one way. That is not to say that what is there is in any way inadequate. It is just to say that if we are going from a narrative standpoint to make these issues really central then --

DR. FREEMAN: To make sure I understand. Are you saying that it is perhaps too dense and what we need to do is perhaps if we are going to also try to limit it in pages is drop some stuff and then add or expand on the more important things?

DR. CASSELL: Well, I do not think you can do that. I do not think that is the problem. The way it is now from my reading it, it is more like a brief than it is like a narrative chapter.

MS. KATZ: Are you talking about Chapter 2 or Chapter 1?

DR. CASSELL: Pardon me?

MS. KATZ: Chapter 2 or Chapter 1?

DR. CASSELL: Chapter 1. And it is just that all people are reading and that is the thing. You know, you can get caught up in all the footnotes and the risks and all the stuff, and you have

got --

MS. CHARO: Actually --

DR. CASSELL: -- except nobody will read it.

MS. CHARO: -- you know what another possible cut on this might be, considering the audience, to eliminate from the main body of the narrative almost all of the discussion of the methodology, which now is in there, in which you discuss some of the difficulties in obtaining information and the variation in the quality of the responses that were received and how that then drove the structuring of your surveys and interviews.

Because what you want for the audience that is going to read the narrative is going to be the punch line and the punch line is federal agencies, you have 17 out of X number of federal agencies that have adopted the Common Rule on human subjects protection. And 25 percent of them -- I am just throwing numbers out because there are no numbers in there. These are invented numbers, all right.

Twenty-five percent of them either do not know that the rule applies to them or do not know how to apply the rule and in either event certainly they do not have any personnel devoted to it.

Now on the fortunate side they also seem to be the agencies that do not do a whole lot of research. But on the unfortunate side we do not have any way of accounting for what research they are doing and whether or not there has been a problem.

Seventy-five percent do have the rule.

You know, you go for the conclusions only in the narrative and then put all the methodological issues that are really things that you know intimately at the staff level but that are really very valuable to somebody who wants to critique the conclusions closely but not are valuable for the person who simply wants to get the take home message.

DR. CASSELL: That is what I meant by being close to in the narrative. You have got all this stuff and you have worked so hard to get it and you are so close to it that that is what happens to it.

I also think the issues that you bring up, which we find to be valid, was that many of them do not know what research is.

MS. CHARO: Right.

DR. CASSELL: I think it is important, really important, because the community in this building never gives that a thought. They were born and raised on it.

MS. KATZ: I think part of what can happen now when we get a really close look at the data is to go back and, you know, put some of that in. As you said, you always write your summary after you have looked at everything. The introduction should, in essence, be the last thing you write.

DR. CASSELL: Right.

MS. KATZ: Because you do not really know what you would want to say until you look at the data. But I think that is an excellent point.

DR. CHILDRESS: Okay. Commissioners, subcommittee members, staff, we thank you all very, very much for the tremendous and, I know, indeed heroic --

DR. CASSELL: Really the effort in this and the amount of work and the amount you got out, you know, the chance of someone saying before this how are you going to get all this, you are never going to get all this stuff, you got it.

DR. CHILDRESS: Before we break in just a moment I certainly would just like to invite -- there are several people I am sure that have been interviewed and so forth -- if there are any thoughts that any people in the audience have? This is a quick chance for public comment. If there is any comment on the discussion we have had. We have obviously ended on the decisionally impaired subjects, which was the major focus of our work today, but if there is any comment on this that you would like to address to the subcommittee we would be glad to hear anyone.

DR. FREEMAN: Jim, I have the first one. There are several people here who have participated and responded to us. They have done a heck of a lot of work added to their usual job to reply to NBAC. I think even in agencies that have -- we would characterize in the Category 4 have been helpful to us and certainly those that in the other categories. So they also deserve a lot of thanks and I thank them all.

DR. CHILDRESS: We join you in that.

Does anyone? Yes?

DR. PRINCE: I would like to ditto what you have said about the prisoners because we have major research going on by psychiatrists in Cincinnati in the prisons and there is no protection at all. They transport them from the prison to a psychiatric hospital for the mentally ill and then keep them there. So it is awesome to me and there is no where to go.

I do not bring this up or say this to be threatening, it is more to show you from Midwest America, you know, what brought me here and I think what brought these other people here, and that is that we have been faced with a government that is perfect at controlling perceptions and offers no access to justice.

Before I left I had someone come up to me and say, "You know, we have Patriot meetings every Tuesday night. We have ten groups meeting in Cincinnati of Patriot meetings. You should come. You should come."

Well, on the other Tuesday night the group that I tried to go to was the Baptist ministers which are meeting with the Black Muslims. They brought Louis Farakhan to Cincinnati last week. It is a terrible dilemma.

What you do not have is the voice of the people. You do not hear us. We cannot be listened to. I have gone to federal court and it was in an orderly way with the help of the state, the politicians, the business, the hospital, it was kept out of the papers, I was never interviewed, and it went on for two years, and

the documentation that I have and what they were doing is astounding. They were taking our blood out of us in the middle of the night and they would put other blood back in.

So we need justice. We do not need -- we need to be heard. We need a voice.

DR. CHILDRESS: Thank you very much.

Other responses?

Well, we thank all of you for your patience as much as anything else today.

(Whereupon, the meeting was concluded at 5:11 p.m.)

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