DEPARTMENT OF HEALTH AND HUMAN SERVICES

FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

PEDIATRIC SUBCOMMITTEE

OF THE ANTI-INFECTIVE DRUGS ADVISORY COMMITTEE

Monday, September 11, 2000

8:00 a.m.

Hyatt Regency Bethesda One Bethesda Metro Center
Bethesda, Maryland

PARTICIPANTS

P. Joan Chesney, M.D., Chairperson
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Richard Gorman, M.D., FAAP
Mark Hudak, M.D.
Naomi Luban, M.D.
Robert Nelson, M.D., Ph.D.
Victor Santana, M.D.

GUESTS AND GUEST SPEAKERS

Jeffrey R. Botkin, M.D., M.P.H. (a.m.)
Professor Francis Crawley (a.m.)
Susan Ellenberg, Ph.D. Ralph Kauffman M.D.
Richard Malone, M.D. (p.m. session) Mark Riddle, M.D.
Neal Ryan, M.D. (p.m. session) Steven
Spielberg, M.D., Ph.D. Robert Ward, M.D.,
FAAP, FCP
Charles Weijer, M.D., Ph.D. (a.m. session) Benjamin
Wilfond, M.D.
Peter Wolff, M.D. (a.m. session)
Dr. Barbara van Zwieten-Boot (a.m. session)
Benedetto Vitiello, M.D. (p.m. session)

FDA

Russell Katz, M.D. (p.m. session)
Tom Laughren, M.D. (p.m. session) Dianne Murphy,
M.D.
Rosemary Roberts, M.D. William J. Rodriguez, M.D.
Robert Temple, M.D.

C O N T E N T S

C O N T E N T S (Continued)

P R O C E E D I N G S

MORNING SESSION - ETHICAL ISSUES

Call to Order/Introductions

DR. CHESNEY: Good morning and welcome to what we look forward to be a very, very interesting two days for very different subjects.

Just a couple of housekeeping issues. The first one is when you turn on the microphone by pushing the green button, if you could please give your name before you ask your question or make your comment, which makes it easy for the person who is transcribing the information.

I would like to start by having everybody introduce themselves and maybe we could start down at this end with Dr. Rodriguez.

DR. RODRIGUEZ: I am Bill Rodriguez. I am currently a pediatric science/director adviser at the CDER, and hopefully trying to work in the pediatric initiatives.

DR. MURPHY: I am Dianne Murphy. I am the Associate Director for Pediatrics at the Center for Drugs.

DR. ROBERTS: Rosemary Roberts. I am a member of the pediatrics team.

DR. GELLER: Barbara Geller. I am a Professor of Psychiatry at Washington University in St. Louis.

DR. LUBAN: Naomi Luban. I am a pediatric hematologist/oncologist. I have a primary interest in

transfusion medicine, and I am Professor of Pathology and Pediatrics at George Washington practicing out of Children's Hospital.

DR. SANTANA: I am Victor Santana. I am a pediatric oncologist from St. Jude's Children's Research Hospital in Memphis, Tennessee.

DR. FOST: Norm Fost, pediatrician, Director of the Medical Ethics Program and chair the IRB at the University of Wisconsin in Madison.

DR. RODVOLD: Keith Rodvold, Professor of Pharmacy Practice, Colleges of Pharmacy and Medicine, University of Illinois at Chicago.

DR. HUDAK: I am Mark Hudak. I am a neonatologist and Professor of Pediatrics, University of Florida at Jacksonville.

DR. NELSON: Robert Nelson, I am a pediatric critical care physician at Children's Hospital, Philadelphia, and I am the Director of their Research Regulatory Affairs Office.

DR. CHESNEY: Joan Chesney. I am Professor of Pediatrics at the University of Tennessee in Memphis, and also in Academic Affairs at St. Jude.

MS. PETERSON: I am Jayne Peterson. I am the Executive Secretary of the Pediatric Subcommittee for FDA.

DR. FINK: Bob Fink, Professor of Pediatrics and

Pediatric Pulmonology of Children's National Medical Center in Washington, D.C.

DR. FUCHS: Susan Fuchs, Associate Professor of Pediatrics, Associate Director of Pediatric Emergency Medicine at Children's Memorial Hospital in Chicago, Illinois.

DR. GORMAN: Richard Gorman, Clinical Professor of Pediatrics at the University of Maryland and in private practice in Maryland.

DR. DANFORD: I am Dave Danford. I am a pediatric cardiologist at University of Nebraska Medical Center and Creighton University in Omaha.

DR. O'FALLON: Judith O'Fallon, Professor of Biostatistics at the Mayo Clinic, group statistician for the North Central Cancer Treatment Group.

DR. WOLFF: Peter Wolff, Chair of The Children's Hospital, the one in Boston, of the IRB.

DR. WILFOND: Ben Wilfond. I am a pediatric pulmonologist at the National Human Genome Research Institute, where I am also the Associate Chair of the IRB, and also a member of the Bioethics Department.

DR. WARD: I am Bob Ward, Professor of Pediatrics, University of Utah, and a neonatologist, and I chair the Committee on Drugs for the Academy of Pediatrics.

DR. SPIELBERG: Steven Spielberg. I am head of

Pediatric Drug Development at Johnson & Johnson representing PhRMA.

DR. KAUFFMAN: Ralph Kauffman. I am Professor of Pediatrics and Pharmacology at the University of Missouri at Kansas City, and Director of Medical Research at the Children's Hospital in Kansas City.

DR. BOTKIN: I am Jeff Botkin, Professor of Pediatrics and Medical Ethics at the University of Utah.

DR. CHESNEY: Thank you very much.

I would like to introduce Dianne Murphy who everybody knows already, Associate Director of Pediatrics for the Center for Drug Evaluation and Research.

I am sorry. Jayne has to give the Conflict of Interest Statement. My apologies.

Conflict of Interest Statement

MS. PETERSON: The following announcement addresses the issue of conflict of interest with regard to this meeting and is made a part of the record to preclude even the appearance of such at this meeting. Based on the submitted agenda for the meeting and all financial interests reported by the subcommittee participants, it has been determined that since the issues to be discussed by the Subcommittee will not have a unique impact on any particular firm or product but, rather, may have widespread implications to all similar products, in accordance with 18

USC 208B, general matters waivers have been granted to each special government employee participating in today's meeting.

A copy of this waiver statement may be obtained by submitting a written request to the Agency's Freedom of Information Office, Room 12A30, of the Parklawn Building.

With respect to FDA's invited guests and guest speakers, Dr. Ralph Kauffman, Dr. Steven Spielberg, and Dr. Robert Ward have reported interests which we believe should be made public to allow the participants to objectively evaluate their comments.

Dr. Kauffman would like to disclose that he has grants with Bristol-Myers Squibb and is involved in research for Bristol-Myers Squibb, Astra, Zeneca, Janssen, Merck, R.W. Johnson, and Aventis, and is a scientific adviser for Bristol-Myers Squibb, Johnson & Johnson, and for Purdue Pharma.

Dr. Spielberg would like to disclose that he is an employee of Johnson & Johnson. Dr. Ward would like to disclose that he owns stock in Ascent Pediatrics and Viropharma. He has grants with Wyeth-Ayerst, Novartis, Ascent Pediatrics, Aventis Pharmaceuticals, and Sepracor, and he receives consulting fees from Janssen Pharmaceutical and is a scientific adviser for McNeil Consumer Products.

In the event that the discussions involve any

other products or firms not already on the agenda, for which an FDA participant has a financial interest, the participants are aware of the need to exclude themselves from such involvement and their exclusion will be noted for the record.

With respect to all other participants, we ask, in the interest of fairness, that they address any current or previous financial involvement with any firm whose products they may wish to comment upon.

Thank you.

DR. FOST: Joan, I thought I had sent it in. I am a consultant to the PowderJect Vaccine Corporation.

MS. PETERSON: Thank you.

DR. CHESNEY: Any other additions?

[No response.]

DR. CHESNEY: Dr. Dianne Murphy will give us our mission for this first session.

Welcome and Review of Meeting Agenda/
Background Information and Overview

DR. MURPHY: My tasks are three this morning, first, to welcome you most sincerely. We appreciate the thoughtful comments that I know we will receive today, as we did in November.

Secondly, is to go over how we hope the day will progress, and, thirdly, is to provide an introduction to the

ethical discussion that we will have this morning.

[Slide.]

During the morning and early afternoon, we will address the ethical issues attendant in the conduct of pediatric clinical trials, utilizing the placebo arm in the trial design.

We are very fortunate to have, not only the majority of the ethicists who participated in last November's Advisory Committee meeting, which I will update you on in a moment, but also to have additional expertise with us today.

I would like to recognize Dr. Barbara van Zwieten-Boot, who is the Efficacy Coordinator of the Medicines Evaluation Board in the Netherlands and the Vice Chair of the Efficacy Working Part of the Committee of Proprietary Medicinal Products.

We would also like to recognize Dr. Charles Weijer, who is a bioethicist and Assistant Professor of Medicine at Dalhousie University, Halifax, Nova Scotia, and Professor Francis Crawley, Chairman of the Ethics Working Party, European Forum for Good Clinical Practice and a member of the Ethics Working Group, Confederation of European Specialists in Pediatrics.

We sincerely thank you for being here with us this morning.

I have already been asked if the examples that you have been sent are real cases, and the answer is yes. As we did in November, we have tried to bring to you issues that the FDA is dealing with today, yesterday, and tomorrow, and we will speak a little bit more just before we go into the questions as to how we would like you to think about them.

[Slide.]

So, why are we here? As of September, the FDA, under the Food and Drug Modernization Act, Section 111, has been actively involved in issuing written requests for products to be studied in children.

I wanted to provide you a quick overview as to what that means. That means that we have issued 157 written requests that would involve 332 studies. We anticipate approximately 85 percent of these studies have or will be conducted after discussing this with the various sponsors to whom these written requests have been issued.

That means that at least 282 of these studies should be conducted. We know that of these studies that we have asked for, 164 of those specify the number of children, the remainder do not. Of those 164, the minimum number of children who would need to be enrolled in clinical trials to complete these studies would be 20,000 children.

[Slide.]

So, that was really a variation upon the theme

about why we were here in November. I wanted to quickly bring the committee up to date as to the results of their discussion in November, so that we can use that as an introduction, if you will, to our process today.

The question in November fundamentally was should children participate in clinical trials which will not provide a direct benefit to the child, or the other way it has been phrased is should normal volunteers participate in pediatric trials.

[Slide.]

This is, just so everyone will know, that we have been busy since the last meeting. The consensus statement that was derived from the discussion, which I have three slides on this, for a day-long discussion with wonderful give and take, and controversy and thoughtfulness, and we have managed to come down to what we think is a consensus statement of what was said at that meeting, which is that, in general, pediatric studies should be conducted in subjects who may benefit from participation in the trial.

Usually, this implies the subject has or is susceptible to the disease under study, and the Advisory Committee utilized a broad definition of potential benefit, for example, any child has the potential to benefit from a treatment of otitis.

[Slide.]

In general, children who can give assent should be enrolled in a study in preference to, or prior to, children who cannot give assent. Careful consideration must be given to the importance of the potential benefit of the study. In certain circumstances, the potential benefit that may be derived from studying children who cannot give assent may override the preference for enrolling assenting children first.

[Slide.]

The third point which we felt was a pretty universal consensus was that the FDA should adopt the principles described in Subpart D, Additional Protections for Children Involved as Subjects in Research. The blue part is where it is in the Federal Register.

This recommendation was also endorsed by the American Academy of Pediatrics and PhRMA. Note that the Pediatric Ethics Working Group agreed that it is appropriate for FDA to consider adoption of a similar statement, and a committee has been established to address this issue.

[Slide.]

The group that is involved in this, just to give you an idea of the breadth of the involvement at the agency, involves somebody from Anti-Infectives where we always classically, traditionally had a number of pediatric trials, the Pediatric Team, the Office of the Chief Counsel, the

Regulatory Policy Staff, individuals from Oncology Division, the Office of Regulatory Affairs, the Office of Science Coordination and Communication, somebody from our Devices Center and our Biologic Center, in addition to the Division of Special Investigations.

[Slide.]

At this point, this group is working to incorporate the principles of Health and Human Services' regulations into 45 CFR Part 46, Subpart D, and they are diligently working to coordinate with HHS in the Office for Human Research Protections to ensure a consistent integration of standards at this point.

[Slide.]

Now, I thought of all the things I could say to bring us to the issue of placebo-controlled trials. I think sometimes revisiting history and telling a story may be the best way to bring us to our discussion this morning.

An example I am going to take is from a book by Thomas Maeder on Adverse Reactions written in 1994. The first sentence in that book says, "The Study of Chloramphenicol is the study of modern medicines."

When you read this book, the entire book is basically about the story of chloramphenicol. You could list statements directly out of it, the majority of them, and apply them to today. Many things are very similar.

This product was the wonder drug of its time with few side effects thought to be attendant to it. As a matter of fact, that was one of its important characteristics. It was one of the first oral broad-spectrum antibiotics, and was available to treat many diseases that did not have appropriate or a therapy as useful as far as administration - typhoid, typhus, and gram-negative and H. flu meningitis.

At the time of its approval, the risk-benefit balance was very much on the side of the benefit of this therapy. After approval, it was associated with a rare but fatal hemolytic adverse event, aplastic anemia. Later, it was shown to cause gray baby syndrome frequently resulting in death in infants that were treated.

This was later shown to be due to the immaturity of the liver and its inability to metabolize the drug, so that blood levels reached basically toxic levels. At the time, this therapy, treatment of antibiotics including chloramphenicol were a recommendation by the American Academy of Pediatrics and other professional groups including for the treatment of a premature infant who was born after 24 hours of rupture of membranes because of the high morbidity and mortality that was associated with that group at that time.

[Slide.]

In an effort to try to define what was happening

once cases began occurring, a trial was designed. That trial was led by Dr. Hodgman and her colleagues at a university in the West, established a research protocol according to which, for one year, from March of 1958 to February of 1959, all premature infants delivered at the hospital 24 or more hours after rupture of membranes would be assigned to one of four experimental groups. Remember, it was considered that this was a group at high risk for morbidity and mortality.

One group was to receive no antibiotics. This was not the standard of care. The next group was to receive intramuscular injections of chloramphenicol, the third group was to receive procaine penicillin and streptomycin, and the fourth group was to receive all three antibiotics.

The groups without chloramphenicol are Groups 1 and Groups 3.

[Slide.]

The experimental protocol was reviewed by the hospital research committee. The only objection at that time was whether or not it was ethical to include a "not treatment" group, which by prevailing standards would subject the infants to increased risk.

[Slide.]

This is at the end of the study. If you remember now it is a year later, February 1959, 126 newborn infants

were enrolled in the experiment, of which 52, or 41 percent, had died. This was high.

The death rates in Groups 1 and 3, those given either nothing or penicillin and streptomycin, were 19 percent and 18 percent. In the chloramphenicol group, 60 percent died. Among those given chloramphenicol and the other antibiotics, the death rate was 68 percent.

[Slide.]

Some people found the experiment ghostly." This is all quoted. "Even in days when informed consent and patients' rights were not issues they have become today, Dr. Wideman of Alabama wrote that their study was one of the most horrifying examples of professional misbehavior he had ever encountered."

[Slide.]

"Dr. Hodgman 35 years later herself says that Dr. Wideman is right. We had a goal when we started; we were going to study X number of babies. But it was becoming obvious that chloramphenicol wasn't good for these babies. We discussed stopping the study early, and the decision was made that unless you have convincing evidence, nobody is going to believe you."

This is one of the questions that we are going to be asking you to address today, which is use of data and safety monitoring boards or other mechanisms to ensure the

safety of the children in these trials.

[Slide.]

In 1972, Dr. Hodgman was criticized by Senator Edward Kennedy for her human experimentation and compared her to the investigators in Tuskegee, Alabama, who had knowingly withheld treatment from 400 black men with syphilis. At first, oddly enough, she was criticized for withholding needed drugs from the high-risk infants in the no treatment control arm, but after the Senator's staff got the facts"--I am quoting--"she was criticized for administering chloramphenicol to the two test groups."

I have gone through this because I do believe at the end of the day that we will not have a consensus. I believe we are here for a discussion.

[Slide.]

Because I think it is still critical to realize that unless you have convincing evidence, nobody is going to believe you, how do we do that in a way that protects the children who are enrolled in these trials?

Thank you. I look forward to your discussion.

Part 1: The Ethics of Placebo-Controlled Clinical Trials in Children

Open Public Hearing

DR. CHESNEY: We don't have anybody who has registered as wanting to comment, but this is time if there

is anybody in the room who would like to make a comment concerning the issue of ethics of placebo-controlled clinical trials, please feel free to come up to the microphone.

[No response.]

DR. CHESNEY: I guess we don't have anybody who does want to make a comment at this time, so we will go ahead and hear from Dr. Temple, who is Director of the Office of Medical Policy. We were provided several articles by Dr. Temple in our reading before this meeting, so we look forward to hearing from him in person, an overview of placebo-controlled trial design: benefits and difficulties.

Overview of Placebo-Controlled Trial Design:
Benefits and Difficulties

[Slide.]

DR. TEMPLE: I am going to talk today about the use of placebos in clinical trials in general, that is, issues not particularly related to pediatric studies and what the problems are with alternative designs like active controls, and then talk about some study design modifications that are compatible with reaching a solid conclusion, but that may make the trials more comfortable when pediatric patients are involved or indeed when adults are involved.

So, I will talk a little about the ethical issues

in general, problems with active control non-inferiority studies, and some design modifications that may help.

[Slide.]

I just want to keep three different cases in mind regarding the use of placebos, one, where there is no available therapy at all, usually people don't object to a placebo control; when there is well-established effective therapy for the particular people involved in the study, that is when the problem arises, and that is the situation I am going to discuss.

In adults at least, use of placebo or placebo with an active control, that is, three-arm study, is generally acceptable in symptomatic patients, but it is not acceptable when denial or deferral of therapy leads to harm, like death or irreversible morbidity.

Whether that same conclusion is equally applicable to children where the consent process is different at least needs to be discussed. I am not going to discuss that, that is for you, but it remains true for reasons I will explain, that in many of these situations anyway, you still need a placebo to have an informative study.

[Slide.]

But in that case, there may be study design changes that will make the whole thing somewhat more comfortable, but still lead to adequate data.

Finally, a difficult problem and one that I won't address in detail is suppose there is well-established therapy in adults. I mean we know antihypertensive therapy is good for adults, but not children, and the therapy is potentially life saving.

When is it legitimate to test those outcomes in the new group in the face of the known adult benefit, that is, there may be very strong prior? Again, I think that is a big problem, but I am not going to have that much to say about it.

[Slide.]

The debate about placebo has hinged on the following question: When there is known effective therapy for a condition, is it or when is it ethical to deny this treatment to some patients in a clinical trial?

This question arises at least partly because of a phrase in the Declaration of Helsinki, 1975 version, that says in any medical study, every patient including those of a control group, if there is one, should be assured of the best proven diagnostic and therapeutic method.

Now, what exactly that meant has been considerably debated, and you would have thought it should matter what condition is being treated.

[Slide.]

Some people, notably Rothman and Michaels writing

in about 1975 in The New England Journal contend that the Declaration has to be read literally and absolutely, and therefore, the condition being treated is irrelevant, and Dr. Rothman says this explicitly.

So, he thinks there can't be placebo-controlled trials involved in this because we have a treatment in seasonal allergic rhinitis because there are lots of antihistamines, headache, because we have lots of drugs, insomnia, anxiety, outpatient depression, obsessive compulsive disease.

Unfortunately, the phrasing in the Declaration would bar any trial, even active comparisons, when there is a known existing therapy because the people randomized to the new drug aren't getting the best available therapy, so it seems unlikely that they could have meant that literally.

What they said they meant when they added that section is that they wanted physicians participating in trials to be aware that there is a patient in there, and that if they need therapy, they are supposed to get it. It is not clear that they meant that there shouldn't be any more placebos, and they certainly didn't suggest that in any of the commentary.

[Slide.]

A recently accepted ICH guideline called "E-10" says essentially that patients can be asked to participate

in placebo-controlled trials even if there is existing therapy when the risk of lack of treatment is only discomfort.

Now, people will have their limits on how much discomfort feels good. Patients in a trial obviously have to be free to leave it at any time without penalty, and the examples given in the document, it is actually beyond developing, it has now been accepted by all three regions in the ICH, generally, this applies to most psychiatric conditions, such as outpatient depression, OCD, panic disorder, anxiety, angina, and a large number of other symptomatic conclusions where therapy is not known to improve outcome.

[Slide.]

Just quickly, there are a lot of situations where you can't use placebos, you can't deny people life-saving therapy with thrombolytics, beta blockers, aspirin post-infarction, ACE inhibitors in almost any situation involving ventricular dysfunction, antibiotic prophylaxis in "dirty surgery," and so on.

[Slide.]

Then, people get into arguments about whether therapy is in fact morbidity preventing or life-saving. There is a current debate about the use of placebos in trials in schizophrenia, whether you think a hypertension

trial is okay probably depends on its duration.

There has been criticism in placebo-controlled trials of the use of antiemetics in severely emetogenic cancer chemotherapy, probably because of fear that the therapy won't be delivered appropriately.

You could argue about whether thrombolytics should be used after 12 hours. There is clear evidence earlier, and whether aspirin is effective in primary prevention could be the subject of a long debate.

[Slide.]

The question is why are they needed. It isn't really placebos, it is really a trial that shows the difference between treatments as opposed to a trial that fails to show a difference or it's perfectly okay to beat an active treatment, that's informative, or to show a dose response, that's informative, too.

[Slide.]

The problems associated with trials designed to show equivalence, that is, that the new therapy is not worse than the previous therapy or not worse by some amount are three. One, there is a historical assumption, that is, of assay sensitivity. I will explain that further, but basically, that is the assumption that the trial could have distinguished effective from ineffective therapies.

Another problem is that there is some lack of

incentive to doing a really good trial when the purpose of the trial is not to show a difference, and sometimes trials can get very large, but three is not the major problem usually. It might be in the pediatric setting.

[Slide.]

These trials, the trials in which the goal was not to beat the control group, but to show that you weren't inferior to it, were once called equivalence trials. They are now called non-inferiority trials because of increased sophistication about these things.

The naive approach was you compare the new and the control drug. If there is no difference, you say, okay, the new drug works. The problem with that is that increase in variance alone, such as making the study too small, will create a success, so that is undesirable.

A more sophisticated design is the non-inferiority design, which specifies as a null hypothesis the new drug is inferior by some margin called M, and then test this significantly. If the 95 percent confidence interval for the upper bound of the inferiority of the new trial is less than M, that is, if it couldn't be more inferior than the margin, then, the null hypothesis is rejected.

It should be noted that if the confidence interval is very wide, if you made your study too small, the study will not declare non-inferiority inappropriately, so that is

good. It solves the size variance problem, but it does not assure assay sensitivity.

[Slide.]

So, the fundamental question in either equivalence or non-inferiority trial is this: Did the active control drug have an effect of the size expected in the trial that was carried out? If it didn't, equivalence or non-inferiority, by the expected amount of that effect, is not meaningful. The equivalent or non-inferior drug might have no effect at all.

[Slide.]

Assay sensitivity is the ability of a specific trial to show a difference of a specified size between treatments, if there is one, and that can be affected by the population you put into the trial. Maybe these are non-responders, for example. By the quality of the study, for example, if no one takes the drug or if the therapies are mixed up, you are not likely to show a difference, and if the study is too small, but that is solved by the non-inferiority design.

[Slide.]

It is worth noting that in a trial intended to show a difference between treatments, the assay sensitivity problem takes care of itself, at least from a regulator's point of view. A successful trial did have assay

sensitivity, a failed trial may or may not, but we don't approve the drug by mistake, so we are comfortable. The therapy, of course, is not available, and that is a possible problem.

Many sponsors now in the situations where assay sensitivity can't be assured include an active control as an internal standard. Then, you can tell the difference between a failed study, that is, neither drug, control or the new drug, was superior to placebo and a failed drug. The control drug was superior, but the new drug was not.

[Slide.]

Remember, in the superiority trial that is successful, you have assured yourself of assay sensitivity, but in a non-inferiority trial, assay sensitivity is not directly measured in the trial. That is, the trial does not itself show the study's ability to distinguish active from inactive therapy, so you have to deduce the presence of assay sensitivity, and you basically do that based on historical experience showing something called sensitivity to drug effects, which we define I think in a later slide as historical evidence that, in general, good trials could distinguish active from inactive drugs.

In addition to that, however, one has to look very closely at the study quality and particularly, importantly, you have to make sure that the current trial is very similar

to the trials that did show assay sensitivity in the past, a problem because medicine marches on, and you may not be able to keep therapies the same. Again, a three-arm trial is a really good thing.

[Slide.]

So, sensitivity to drug effect is a historically-based conclusion that properly designed trials with a specific active drug or perhaps a group of related drugs reliably show an effect of some defined size.

Generally, you look at all the placebo-controlled trials that you know about and see that they were successful. Sensitivity to drug effects is an abstract conclusion about a well-designed trial, assay sensitivity is a conclusion about the specific trial.

[Slide.]

If well conducted and designed placebo-controlled trials more than occasionally show no difference between the active control and placebo, perhaps without some good explanation, sensitivity to drug effects doesn't exist, and one cannot conclude a new drug is effective from a non-inferiority trial of similar design and conduct.

[Slide.]

Sensitivity to drug effects is, as I said, shown by placebo-controlled trials, the situations in which it is hard to show, that is, where trials regularly fail to beat

placebo, are when the drug effects are small to variable and often when there is a substantial and variable improvement in the placebo group, that makes life difficult.

[Slide.]

Anyway, bottom line, if you can't be very sure that the positive control in the study would have beaten the placebo group had one been present, the fundamental assumption of the positive control or equivalence or non-inferiority study can't be made, and that design is not usable.

[Slide.]

Just some examples of situations. This is all based on adult data, but it is equally true at least in depression for children, current drugs lack sensitivity to drug effect. That is, good trials regularly don't show anything, usually for reasons we don't understand.

That is true in depression. It is true in anxiety. It is true in dementia. It is true in symptomatic congestive heart failure, perhaps surprising. It is definitely true in seasonal allergies. GERD is notoriously difficult to show anything on.

Most of the studies of post-infarction beta blockade have failed to distinguish drug from placebo. It is possible that is a matter of size, but nowadays with people getting aspirin and then all kinds of other stuff in

addition, it is very unclear what the effect size would be. Post-infarction aspirin is widely accepted as being useful, but as probably everybody knows, the largest trial of that intervention ever carried out in the United States failed to show anything, in fact, leans slightly the wrong way on survival.

[Slide.]

It isn't that the controls aren't effective. We know antidepressants, antilytics, antihistamines, et cetera, work. They are better than placebo far more than the predicted roughly 1 in 40. It is just that you can't exactly define conditions in which they will always work.

[Slide.]

Now, having established that there is sensitivity to drug effects and that you would believe that a study might be successful, you have to choose a non-inferiority margin. Remember, the whole point of a non-inferiority trial is to declare that the new drug is no more than M worse than the old drug, so that is the margin.

The margin can't possibly be any larger than the smallest effect you are willing to presume the control drug has in this study. That is as big as it can be. In fact, if you then excluded that margin, you would be sure that the new drug has any effect at all, that is, is better than placebo.

Usually, in active control trials, people want to know something more than that. So, for example, in thrombolytic trials, the Center for Biologic Evaluation and Research concluded that at least 50 percent of the effect of the control thrombolytic ought to be preserved. So, their margin was half of the effect size that they were pretty sure the control drug would have. Anyway, that is plainly a clinical judgment.

[Slide.]

As I said, the margin could be the entire effect or it could be some smaller part.

[Slide.]

Just to illustrate how this is done, on this axis, I am showing the difference between the control drug and the test drug, so that going up means the control drug is better. You can't probably see them, but there are dotted lines across M1, M2, and M0. This slides needs more work, but anyway, M1 here is the whole effect of the control drug that you are quite sure from historical experience the control drug would have.

M2 is half that, and M0 is supposed to go through the zero line. That means there is no difference between the therapies. If you weren't sure from historical experience that the control drug reliably could be placebo, you would have to use M0. That means only superiority would

be informative.

Just a couple of examples. In this case, and again this is the actual measured difference and this is the made-up confidence interval, in this case, the new drug is non-inferior to half of the 50 percent margin, so that is pretty good evidence that the new drug is effective. It is definitely better than the M1.

In case 2, the point estimate is a little bit higher, so that if the margin was the entire effect of the control agent, it would be an effective agent, but if you had to preserve at least 50 percent of the effect of the control agent, this wouldn't.

The third case, the 95 percent confidence interval is greater than the whole M1. That means there is at least some chance that this drug has no effect at all.

The fourth example shows superiority to the control drug.

The fifth example shows the effect of the large variance. The point estimate actually favors the new drug, but the confidence interval is outside of M1 because it's too small a study.

[Slide.]

Anyway, you have heard this. The assumption of assay sensitivity is not necessarily true for all effective drugs. I am just going to illustrate with a couple of

examples briefly.

[Slide.]

The first slide shows all six trials of a new antidepressant called nomefencine. We were still hiding its name at the time this slide was made. These are all three-arm studies. They have the nomefencine, imipramine, and placebo, but I am not showing you placebo yet.

You can see that some of the trials are fairly small. These are the sample sizes here. These are sort of typical of the time in which they were done. These trials here are very tiny. You wouldn't really expect much from them.

What we are measuring here is change in HAM-D at the end of four weeks, a fairly standard measure, and these trials were analyzed using a common baseline for reasons I won't get into.

What is important here is that the six trials show absolutely no difference between the new drug and imipramine. They are almost within a point of each other. So, if you believed in equivalence trials, you would say, well, this certainly shows it.

[Slide.]

The trouble is five out of the six trials had no ability to detect anything, so that in Trial 1, placebo is practically on top of the new drug and imipramine. The same

with the second trial. The same with the third trial. The placebo is actually slightly better.

Only this tiny little trial with seven or eight people per group had assay sensitivity, had some ability to distinguish active drugs from inactive drugs, so the placebo hardly changed from baseline at all, and the new drugs worked like gangbusters. The next two show nothing at all.

So, five out of the six trials were uninformative. It doesn't mean the drug works, it doesn't mean it doesn't work, you just don't learn anything.

[Slide.]

I went back over three years of psychotropic drug experience a couple of years ago. Tom Laughren, who is here, has done that more recently. We get essentially the same results.

This is the rate of studies of reasonable size--you will see the sizes on here--that failed to distinguish active drug from placebo. In many cases, it is not that they were near, you know, 0.07, it's that they didn't show anything.

So, 1 out of 3, venlafaxine controlled release failed. Five out of 10 mirtazipine, 1 out of 1 trazadone. Some of these were the control drugs. Nefazadone, 3 out of 7 failed on nefazadone, actually, 3 out of 5 imipramine. All of the flow release trials of buproprion failed.

Probably the dose was a little low, but it was an effective dose.

[Slide.]

The same thing with antipsychotics, the same thing with OCD.

[Slide.]

Similar in panic.

[Slide.]

Just briefly, Milton Packer, Director of the Center for Heart Failure Research at Columbia, but he is also our advisory committee chairman on the Cardiorenal Advisory Committee, looked at all the FDA reviews for effectiveness in symptomatic heart failure.

What he found, four or five drugs, most of them ACE inhibitors, was that exercise tolerance seemed to be successful less than half the time. That is usually the hallmark. Symptomatic improvement arguably was slightly better, but not consistently. Change in New York Heart Association class was not too consistent. Global looked in some ways most promising, but these are all drugs that unequivocally are effective in heart failure. They improve symptoms, they improve survival, but it is not so easy to show it. All of these trials were large in the neighborhood of 100 or more per treatment arm.

[Slide.]

Just one more point. I won't dwell on this, but when you are showing to show a difference between two therapies, you have to be on best conceivable behavior because many of the kinds of errors you might make will interfere with the ability to show what you want to show because they will increase variance.

Sloppiness can obscure differences. Now, as I said, the non-inferiority design is a protection against certain kinds of sloppiness, like too small, but it doesn't protect against others.

[Slide.]

So, even if sensitivity to drug effects exists for a therapeutic class, you can still undermine the ability of the trial to have shown a difference if there was one by such factors as poor compliance.

[Slide.]

If nobody takes the drug, you can't see a difference. A population that tends to improve spontaneously, this may be the problem in depression where people are much better in the placebo group, or a population that is unusually resistant, use of concomitant medication that interferes with the test or that reduces the extent of potential response, poor diagnostic criteria, that is, patients don't have the actual disease, you can't show a difference if they don't have it. Insensitive measures of

drug effect. Poor quality of measurements, those might increase variance, it might not, it is hard to say, and mixing up the treatments, you might laugh, but that has happened. That guarantees success in the trial.

[Slide.]

In general, these factors that I listed don't affect variance, so they don't make the confidence interval wide, but they can reduce or obliterate the active control versus test differences, that is, they are biased toward the null, which leads to false conclusions of non-inferiority.

It is worth noting that some analytic approaches that are conservative in a different showing trial, like intent to treat, are not conservative in a non-inferiority trial.

[Slide.]

So, the things you ask about a new trial are is the design of this new trial similar to the trials that were successful, is it the same patients, are they treated the same way, has therapy evolved in such a way as to make the effect smaller, that is, is there any new therapy that now has been added, and is the endpoint being measured the one in which the previous trials were successful.

[Slide.]

I think I will skip this. The main point here is that because we are weighing historical evidence as opposed

to measuring assay sensitivity in the immediate trial, one has to make a conservative choice about the margin, and that often leads to relatively large studies.

That is not too big a problem in the adult population, but it might be considered a problem in the pediatric population.

[Slide.]

Just sort of a final reminder. The lack of a difference or non-inferiority by itself does not show anything except non-inferiority. For the non-inferiority trial to also imply effectiveness, which isn't actually measured in the trial, you need a critical additional piece of unmeasured information that is assurance that the active control actually had an effect of the defined size in that study.

[Slide.]

It is worth mentioning that the assay sensitivity question arises when the intent is to compare two drugs. Unless one of the therapies is superior, in which case it is informative, if the objective is to say this is just as good as that one, you have the same problems.

[Slide.]

Just briefly, and then I will spend a couple of minutes on these. Even if a placebo-controlled trial is ethical in a particular situation in adults, it may be

unpleasant for people. They may not want to be in it. The investigators may feel uncomfortable.

So, it is worth thinking about study designs that are still ethically acceptable that might be more appealing than a simple drug versus placebo, things one can do. This is really important to later in the day.

The first situation is the add-on trial. I will go through these quickly, and then I want to go to the proximate. One is the add-on trial, and we will come back to that.

[Slide.]

Beating the standard is always good, and doing a dose response study is informative. Sometimes you can carry out a trial in a population that isn't known to benefit from standard therapy or that has failed on it. I will come back to that.

[Slide.]

One can build early escape provisions into the protocol, so that patients not doing well don't have prolonged exposure to an ineffective therapy. I will come back to that, and you can do a randomized withdrawal study, and I will come back to that.

Could we do the proximate ones now.

[Slide.]

In a lot of situations, when there is known

effective therapy, the only trial you can carry out ethically is an add-on trial. You can't leave ACE inhibitors out of a heart failure regimen anymore, they improve survival, so you can't leave them out, but if you have a new therapy, you can add it to the accepted therapy.

That involves randomization to the standard drug plus the test drug or standard plus placebo, and you can introduce dose response elements into it, and this gives clear evidence of an effect, but unfortunately, no data on monotherapy. Still, you at least know something which is better than knowing nothing.

This is absolutely standard now in antiepileptic pediatric studies where it is generally felt that leaving patients untreated is not acceptable.

[Slide.]

The design here is very simple. They are on a standard therapy for some period of time, or this could either be because they are on it already or because you put them on it in the lead-in period, and then you randomize to the standard plus the drug, there could be several doses, or standard versus placebo, and you show a difference between these two, and then that works.

Sometimes you can actually take the standard therapy away and observe what goes on then, and that is sometimes done in antiepileptic drugs.

[Slide.]

It is sometimes possible to study non-responders to available therapy. That avoids denying somebody anything that they could use. It does give data on a different group that may be less responsive to the therapy if it is of the same pharmacologic class, or they may be non-responsive at all.

Randomizing these patients to drug or placebo does give you information about whether the new drug works. If you really wanted to know whether the drug was superior or superior in non-responders, then, you would need to randomize back to the drug they failed on or the new drug and show superiority. The next slide shows that.

[Slide.]

An important element of design is studies that in one way or another limit duration of exposure to an ineffective treatment. One general concept is early escape or early advance.

Even if a placebo could be used in trials with symptomatic therapies because no harm will come to people, prolonged treatment with an ineffective agent may be uncomfortable and you might find that particularly true in children.

One thing that trials can do is introduce an early escape or an early advance if it is a crossover study, that

is, you move to the next therapy in which patients failing to improve to some defined extent or who worsen at some specified time or at any time, are considered completers or failures. Their last value can then be carried forward for a conventional analysis or the ability to complete can actually be used as an efficacy endpoint.

That was actually the design used to study vasospastic angina with nifedipine, the first approval for that claim. Nobody particularly wanted people having multiple episodes of vasospastic angina, so as soon as they worsened, even for a day, they were considered failures.

[Slide.]

Unfortunately, early escape in a conventional trial may leave too few patients treated for the duration of interest, but you might not like the idea of a very long placebo-controlled trial in children or in anybody else.

One remedy is the randomized withdrawal trial proposed first by Amery in 1975 for angina trials. This is a situation in which people are on the therapy of interest for a long period of time and are seeming to do well, and are then randomly taken off the trial.

This allows long-term exposure without long-term placebo, and this, too, can have early escape provisions. So, it gives information on long-term effects without long-term placebo. You have to worry about the possibility of

withdrawal effects, narcotics or nitrates, or something like that.

It is a trial that is enriched with responders. Only people doing well and responding well are likely to be in the trial, so it might overestimate the effect in naive patients, but it does give you evidence about effectiveness.

As I said, it can have early escape provisions, and if there is an existing open protocol, it eases recruitment. In other words, if there is a large number of people on this drug for one reason or another, and you want to do a trial like this, and can convince people to be in it, all the patients are there, you don't have to recruit them over a long period of time.

So, the nifedipine trial that I described took people who are already on therapy. They were able to do the trial in about three months, whereas, waiting for large numbers of people with vasospastic angina to show up in your office could take a very long time.

[Slide.]

The general design is people are on the drug and they are randomized to either a single dose or several different doses and to placebo.

[Slide.]

Another thing worth thinking about--and we do as part of the Pediatric Rule--one might ask a different

question. Given adult data, it may not be necessary to carry out the same trials in children. You have a strong prior, if you like, and as you know, we are actually allowed to believe the drug works the same way in children as in adults even if there is no evidence other than our own belief or your own belief, so that a simpler, shorter question might be better than that.

Just as an example, in hypertension, the typical adult placebo-controlled trial, just to show that it lowers blood pressure, would run four to 12 weeks, would a one-week trial in children suffice perhaps with a randomized withdrawal trial after a longer period? After all, you are fairly sure it is going to work.

In seasonal allergy trials, very large trials are often needed because of variable pollen and possibly other reasons, but we know that studies in Chambers, in which an antigen is induced, are usually much smaller and much more sensitive, would that be sufficient in the antihistamine case?

Now, we have approved drugs without any studies at all.

[Slide.]

Could one suffice for a drug intended for long-term analgesic use in children even with a relatively small, short study in adults given our knowledge that the drug has

long-term effectiveness in adults? All questions that need to be answered case by case.

That's it. On some other slides, which I won't show, I had some examples of trials that actually used some of these designs, but I think that is not the important question here, so I think I won't show them.

Anyway, the active controlled trial is often uninformative, and that poses a real problem because it is not a good thing to approve a drug when it doesn't actually work. Our hope is that we can have studies that are interpretable and that yet feel comfortable, and you will discuss this much more I know. Thanks.

DR. CHESNEY: Our next speaker is Dr. Barbara van Zwieten-Boot.

International Perspective on Pediatric Placebo-Controlled Trials

DR. VAN ZWIETEN-BOOT: Good morning.

[Slide.]

First, if you will give me two minutes, I will try and show you where I come from because I understand by now that Europe is somewhat difficult for most people that are not really living there and, even if you do, you still don't understand it.

[Slide.]

Apart from having patients and the doctors and the

pharmaceutical industry, there are, in Europe, three other players in the field of licensing drugs. The member states, which we, at the moment have fifteen, as you know, and two almost, Iceland and Norway; the Commission in Brussels who is a kind of civil servant to the Europe that doesn't exist at the moment, but we do have to have civil servants; and CPMP EMEA which is based in London and is the European licensing authority.

For those products that follow the European route or the central route, you have to go to London. If it is a product that, for one reason or another, follows the national route, you have to go to the member states.

So CPMP is the part where you go for a license and they do the assessment, at least they are responsible for the assessment. CPMP consists of fifteen times two persons, so every member state sends two persons. But you sit there as experts and not as representatives of your country. And there are two more, one from Norway and one from Iceland. And there is a chair which, at the moment, is Professor Alexandre from France.

If you send in your license and your product there, they will appoint two coordinators or a rapporteur/co-rapporteur. They are responsible for doing the assessment. Usually, they fall back on the member states to supply the personnel to do that and it will be

discussed here in London. The EMEA is supportive, both for the legal support, logistics. They support in the meetings, et cetera.

CPMP has a group of working parties, ad hoc or standing working parties, and there is a group that is doing scientific advice which, to some extent, is the same as you do in phase II or phase III discussions with the industry.

Working parties are also coming from the member states so you have fifteen official members and a chair, and a vice-chair in some situations. They are setting up the policy documents. The guidelines are coming from there. Using the guidelines, you then can make your assessment of specific products.

That is where I come from. I work in The Netherlands. I work for the Medicines Evaluation Board in The Netherlands but I am also vice-chair of one of the working parties, the Efficacy Working Party, and an expert to CPMC, so part of my time, I will be in London.

In the working parties, we make European guidelines and we are also involved in the international guidelines, the ICH guidelines, that Dr. Temple just has been talking about and two of them are actually in the handout that the FDA has given to you; E-10, which is the choice of control, and E-11, which is the pediatric guideline.

But all of this that we do here is we make guidelines. CPMP has no opinion. To make it a directive or to have a directive, you have to go to the Commission. If the Commission draws up a directive, then the member states have to put that in law. So, what we do is guidance and companies can follow it or not, although, if they don't, they have to come up with good justification. It is in Brussels that you can have the law. That is the difference between the two.

Then, at the moment, they are working, for instance, on the clinical-trial directive which tries to put the GCP, good clinical-practice guideline, that we have made for ICH in a legal framework because, at the moment, in Europe, it is just a guideline. But we want to have it in a legal framework, so they are working on that.

At the same time, then, they try to regulate more on the European level how to have clinical trials. But one of the things that you see there is that they are very careful not to harmonize ethics because it is thought in Europe that ethics belongs to the member states. It is up to the member state to see, in their domain, what is ethical.

So there is no European harmonization or ethics although there are a lot of discussions going on in Europe about ethics. And that is where Professor Crawley comes

from. But I am here. I am working for the authorities.

[Slide.]

To show you that we have the same problems in Europe as you have here, this is from a recent publication in the British Medical Journal. It was a kind of survey done in five pediatric clinics in Europe; Derby, which is the U.K.; Uppsala is Sweden; Marburg is Germany; Bergamo, Italy; Rotterdam is The Netherlands.

They, for a certain time, followed the prescriptions that were given and, not surprisingly and more or less what you see, too, is that about 50 percent are either unlicensed or off-label. Seven, almost, were unlicensed drug use so, apparently, there were experimental drugs used, and about 39 were off-label use of drugs.

If you look into that publication, you will see that the drugs that were prescribed and that were not off-label for a huge number of prescriptions was parasitimals which, and it is about two-thirds of the patients in these clinics, but some of them were university clinics that received unlicensed or off-label treatment.

So we have a problem here and we have realized it.

[Slide.]

So what are we doing? In Europe, we are in a somewhat different situation than you are because we have to deal with various member states. But what we have done up

to now is we had a European guideline which was written, I think, in '89 and we have updated that in 1997, put more emphasis on the need to do these kinds of trials, when to do them, how to do them. We have, somewhat--in this guideline, there was more emphasis on the need for clinical trials than you will see in E-11, to some extent.

And we gave some guidance what to put into the SPC, which is your datasheet, if you have no trials done. We, because the FDA had their own rules and Japan wanted to have some rules of pediatrics, came up with a discussion in E-11. Dr. Spielberg is here and he knows much more about it than I do. And it is in your handout. You can see what kind of data were discussed there.

At the same time, in the EU, we address certain therapeutic areas and we start up, now, to put in those guidances there, where it is relevant, some comments on the clinical trials in children.

But it is curious to see how difficult it is to get that starting. It is not only industry that does not want to do it, it is also we, ourselves, the assessors and the authorities that have to switch and have to start thinking that it is really necessary, if there is a situation where we ask it yes or no.

And then, because this is our old guideline, there is a discussion starting now in Brussels whether or not we

need to have something like a directive put in law, maybe along the lines that the FDA has done here, or maybe somewhat different. That has certainly not crystallized out at the moment, but we are discussing it.

France has the presidency at the moment for the EU. We switch presidents every six months. France has put, as one of the things that they want to accomplish during the six months, that there will be some more emphasis on pediatric trials and they have circulated a memorandum to that extent which is being discussed, I would say, in two weeks time.

All of this, or most of this, is about new chemical entities or a line extension to release new products. What we still have to address actually will be very difficult but that is something that you probably have seen here also is what to do with the products we have already licensed, what kind of data do we need there, to come up with evidence-based advice in the datasheet or SPC.

[Slide.]

So that is where we are. What if you are going to develop a drug, then? The purpose of clinical development in children, you may say that is self-evident. But what I would like to discuss with you, or maybe in the discussion for this morning, is that if you read E-11, one of the basics there is what kind of data do you need, when. To

what extent can you extrapolate or not?

Is it always necessary, just like Dr. Temple just said, to have a full-blown program or not? I think that is something that we should take in mind when you are discussing the need or not for placebo.

In the case--and this is, more or less, coming from E-11--the disease is typical for children, the efficacy and safety have to be shown. If it is a disease that is only in children, like Lennox-Gastaut, for instance, if you want to go to the antiepileptics or ADRS in premature children, then you need to show it just like you have in development in adults.

Usually, you can't extrapolate for adults because they don't have that disease. So you need to have the whole development plan.

If, however, you have a disease that is the same in adults and children, the disease process and the outcome is the same, then the focus of the clinical development should not be the whole program but much more what is the effective dose or dose regimen and what about safety.

The safety we are talking about here is, then, not only the safety that you see in adults but also the specific safety focusing on children like growth, CNS development, learning, behavior and maybe the endocrinological process when puberty starts--certainly, if you are talking about CNS

products this afternoon.

[Slide.]

In E-11, you will see that in the case where the disease is the same for adults and children, some extrapolation from adults to children may be appropriate. This, again, as Dr. Temple said, will be on a case-by-case basis but the considerations you could have are the following.

Sometimes, it could be done on pharmacokinetic data provided that relation between blood levels and efficacy is known. That is very difficult. We know, to some extent, which dose or which blood levels give an effect. But whether or not that is the optimal is something different. Dose-response data are usually very bad in a lot of situations.

But there is a way out if you can show that, then you have pharmacokinetic data, then you can extrapolate your data. You don't need to have, maybe, a clinical trial.

If you don't, you could try and fall back on pharmacodynamic data or studies with a surrogate endpoint if you know that this endpoint is relevant for efficacy. So maybe you could have tumor response instead of going all the way down to the mortality rate if you know already that, for that specific tumor, the drug is effective in adults.

Or you could do, for instance, in asthma, FVE1

trials as we do with salbutamol, or albuterol, as you call it here, instead of doing your full-blown clinical trials and use that as an extrapolation provided that out of these data, you get your dose regimen data.

If not, you have to do clinical studies. But, again, if you already know the drug works in adults, then you might be sufficed to have only one trial instead of the usual program. And, if that trial shows you what you expected, then you will assume that the rest will follow, too.

But, whatever you do, you need to have adequate safety data. And that may be a problem if you only want to have pharmacokinetic data.

[Slide.]

The point is, if you do pharmacokinetics studies, of course, you have advantages. Usually they are small-scale trials and, therefore, you have fast results. They are somewhat larger than we have in the usual volunteer studies in adults because you can't run the same trials. But you usually have data from various children together to get your time curve. It can be done.

But there are disadvantages that maybe you should consider when you try to go that way instead of having a placebo-controlled trial. One, and that is certainly a problem in Europe, is the fact that pharmacokinetic studies

are usually done in a non-therapeutic setting.

We have addressed that point in the DSCP guideline for those of you who want to see it there, but this is an issue in Europe. In my own country, in The Netherlands, there has been, I think, a twenty-year debate in Parliament on the law that would regulate clinical trials in humans. This was one of the big issues; can you have a trial in volunteer children that are healthy or at least don't benefit from the drug they get.

In the end it was yes. I know from my German colleague who told me that it is not allowed in Germany. So it is not easy to go this way if you cannot do the trials because you need separate studies.

Clinical studies, the large advantage, of course, is that you get clinically meaningful results. You can interpret it and you can use it in the clinical practice. You have comparative safety data which makes it much easier for us to understand what the safety problems are, and you do it in a therapeutic setting. For one reason or another, that is easier to do than in a non-therapeutic trial. You shouldn't misunderstand it. This is really a big problem for us.

The disadvantages, of course, are the large numbers. It is a slow process and a choice of comparator.

[Slide.]

There we come, then, in the problem of the placebo. This is from E-10 and it is more or less already discussed by Dr. Temple. If there is no standard treatment available, you can do a placebo-controlled trial although, in some situations, you may choose for a no-treatment control which we see in oncology a lot because the scheme, the dose regimen, is so difficult that it is easier to have not a placebo but a non-treatment control.

Sometimes, what we ask for is superiority over best of care so everybody gets best of care and you are sure that your drug is better than that. There is always the possibility of a dose response. We show that a high concentration or a high dose of the drug is better than the lower dose but it may be discussed whether or not a low dose has not the same ethical implications as the placebo does.

The other is that if standard treatment is available, what are we going to do then. That has just been discussed by Dr. Temple. You can try to do a non-inferiority versus standard but then you need to know something about what he called assay sensitivity, what in 11 is called historical evidence of sensitivity to drug effect which means that you should be quite sure not only that the standard works but that it works in clinical trials and is always, or most of the time, different from placebo.

If you don't know that, you cannot set your

margin. If you cannot set the margin, you cannot do equivalence or non-inferiority trials because the results, you don't know what to do with them. You can't interpret them.

The problem here is in children that we just have said that most of the drugs are used off-label. We know that they work, or we think that they work, or at least they are used and may be standard therapy. But there may be a lack of good data to know what the effect size is. If you don't know the effect size, again, then you run into troubles with setting your margin.

It may be that the margin is set in such a way that you run into the placebo and, therefore, show that your drug may be as effective as the active control but also would have been as effective as placebo if placebo was used.

So there is a very big danger in doing that. And you can only do it if you have sufficient data to justify it. If that is impossible to do, and it might be in more cases than we think, then we come to the superiority versus the standard which we always will accept, all of us. Provided that there are no safety risks on the other side, we will allow it.

If not, then we are back to placebo. As Dr. Temple already has said, there are a variety of possible placebo-controlled designs which might help to resolve some

of the ethical issues, at least make it more acceptable.

The other note is that placebo control, some people seem to think that if you give a placebo, you don't do anything at all. But that is not true. Seeing the high placebo effect in a lot of trials that I got in, sometimes up to 60 to 70 percent, placebo might be a good drug.

But it is not only that. It is also the placebo control doesn't imply the use of rescue medication or palliative medication, depending on the situation, cannot be considered. Of course, you can give morphine in an oncology trial. So it is not that the patient is not treated. He is not treated for that specific area where he is ill.

[Slide.]

So where are we? As far as I can see, certainly, the disease is not the same as for adults. Ethical and methodological considerations are the same for adults and children. Even if efficacy is demonstrated in adults, if, therefore, efficacy in children might be expected, you need to some something about assay sensitivity or historical evidence of sensitivity to drug effects.

It is an awful sentence, but that is the way it was defined in the E-10. You need to know it because, otherwise, you can't draw a conclusion from your trial in the case that a clinical trial is considered necessary. The need for a placebo has to be justified but, also, the need

for an active control. Always, and it not only for children--it is also for adults, but, certainly in children, you have to justify your clinical-trial program.

But if, on methodological grounds, it is said that you need a placebo and that it is the only way to come to a conclusion, then I would say that it would make the acceptance of the placebo higher. There is no law against placebo use in therapeutic trials in the EU. There is in some member states a law against non-therapeutic trials, in general.

[Slide.]

I have picked up two examples, just to give some flavor of what we are talking about. This is from our own database in The Netherlands. Actually, we have, the last ten years or so, accepted about seven new antiepileptic drugs, three of which have no clinical data in children, but we are running trials, at the moment, so I left them out, which gives us four.

You can see that it sometimes takes a long time to go through a process. Here you see a drug that was licensed for adults in 1991 and the children's studies came in 2000. We licensed it in 2000. It took ten years to review the evidence, and I can tell you the drug was used for a long time.

What you also see is that most of the trials are

done as an add-on. There are very few monotherapy studies, only, in this case, we had the monotherapy study against phenytoin and, because of the results, we allowed that as a monotherapy claim. But most of them are in the add-on situation which is a good situation to show an effect of the drug but doesn't help you much further if no further studies are done.

What you also can see is that not only for typical seizure types, like Lennox-Gastaut, placebo-controlled trials were done but also for the partial seizures with or without generalization even though there is a discussion whether or not the partial seizures you see in children are the same as the partial seizures you see in adults.

One of the reasons for that probably is that if you are in an add-on situation, you already have two or three antiepileptics and you add your test drug, pharmacokinetics will not help you because it has become much too difficult to understand what you are doing and, therefore, you get in your placebo-controlled trials.

Now, I realize, this is becoming controversial. This I picked. I must say, this is a typical Dutch example. It is certainly not a European example, but it helped to make a few points later.

Otitis media--this is a quote from the Association or Society of General Practitioners in The Netherlands who

make their own treatment algorithm, and they say that the treatment is symptomatic in all children. That means you give parasitimal and anticongestants if you want, except for children less than six months old and children--you may start antibiotics if, after three days, the symptoms increase or the children are not improving.

But for the usual situations, the GPs start with symptomatic treatment. This is based on the placebo-controlled trial in 1981 from the Dutch GP centers and this is a very large observational study where they found that more than 90 percent of the children could do without antibiotics and were improved after three days

This is from here, I would say, and would show that there is a huge debate going on, at least at that time and I got the impression this morning that it is still going on. The reason I gave this example, even I know it is difficult to do here.

[Slide.]

It is because if there is one area where you could maybe extrapolate on pharmacokinetics, it should be the antibiotics because you know the bacteria it affects and you know there is a relation between the dose or the blood samples and the blood levels and on the effect, and my colleagues in that field tell me you even can predict PK/PD. However, if you do that, you have to know for sure that the

same bacteria or the same strains are in the adults and the children, and in this case, apparently, that is not so.

You also need to know that it is relevant to treat that group with antibiotics, and as I said, in this case, where 90 percent of the children apparently could do without, you have no assay sensitivity, and therefore, it might be difficult to do it without placebo.

A third point I would like to make is that there was a huge willingness of parents and doctors for this kind of trials. The placebo was a reasonable large trial, and the observational studies were almost 5,000 kids, so apparently, if you tell them why we do it, we can do it.

[Slide.]

The conclusion, this is a quote actually from a French document that is now circulating, because as I said, they have taken initiative, and they said that the use of placebo in children raises no more ethical problems than in adults. The use of the placebo, or in brackets, reference product facilitates rigorous evaluation of the effects of a product. It is, in fact, the absence of the evaluation that should be seen as unethical.

Thank you.

DR. CHESNEY: Thank you very much.

We have 10 minutes now for the Committee to ask questions of both Dr. Temple and Dr. van Zwieten-Boot.

Yes, Dr. Nelson.

Questions from the Subcommittee

DR. NELSON: A question for Dr. Temple. The threshold that you offer and in your slides for a placebo to be considered is when the withholding of the effect of treatment would not result in either death or irreversible morbidity.

My question is whether you believe E-10 discussed that issue in the context of pediatrics, and if not, whether it would be appropriate to tackle it in E-11.

DR. TEMPLE: I don't think E-10 really did consider it. It presumed informed consent. That was an important part of its consideration. Informed consent is clearly a different animal in children. So, I think E-11 probably does need to discuss it, but E-10, I don't believe did.

DR. CHESNEY: Yes.

DR. WARD: For Dr. Temple. You proposed using crossover when there was a failure of effect, and how would you handle that statistically, would you then use intention to treat and leave the patient in the original assignment, or would you consider that failure of the original treatment to be an endpoint?

DR. TEMPLE: Well, you can do either of those things. In the example I didn't show, in the nifedipine

vasospastic angina, they count it as an endpoint, inability to complete the one-week trial, and you saw a difference in number who complete.

You would also, however, carry the last observation forward and do a sort of conventional analysis if you allowed people to leave after a certain period of time. I think either could work. There is not so many illustrations as one might like.

DR. CHESNEY: Dr. Wolff.

DR. WOLFF: This is a naive question to you for my information. If there is effective standard treatment, why would one under any circumstance want to--given also the limitations of the non-inferiority design--why would one even engage in such studies other than to put new drug on the market?

DR. TEMPLE: Well, that is an important reason, but there are reasons to have more than one example of a particular drug. I mean in the antibiotic area, for example, each of the drug classes has its own toxicity, and you might well want to know whether a drug with different or less toxicity worked.

Just a classic example. When there were only sedating antihistamines around, you might want a non-sedating antihistamine in children, so they don't sleep through their classes.

Many, many examples. For example, the new antidepressants do not differ in effectiveness from the old antidepressants. They differ markedly in the side effects and tolerability. The same for the new atypical antipsychotics.

There is often reason to have more than one treatment for something.

DR. WOLFF: But that goes into superiority, doesn't it?

DR. TEMPLE: No, even if it's--well, it is superior in tolerability, but the new antipsychotics and antidepressants are not superior in effectiveness to the old ones.

DR. CHESNEY: Dr. Spielberg.

DR. SPIELBERG: Just a brief comment on Dianne's comments on chloramphenicol. I think that story has to put us in awe and make us remember just what we do not know at any time about biology and medicine, but I think there are several more messages in that story that need to be put into this mix.

The first is what was going on at the time that the clinical trial was going on. In fact, chloramphenicol was being rapidly introduced into therapy in nurseries all around the country, particularly at university medical centers, which thought they were smarter than the non-

university centers, so that there was a tremendous amount of non-controlled use going on.

In fact, one of the classic epidemiology studies, which was published just about the same time that the controlled trial came out, showed that at one university hospital, mortality had gone up dramatically compared to non-university hospitals in the same community as a result of the introduction of chloramphenicol.

The second thing was the conventional wisdom was pen-strep, and that study showed that, in fact, pen-strep was no better than placebo, which made us rethink the entire issue of how to manage babies with premature rupture of membranes and how to begin approaching therapeutics in that setting in a somewhat more rational way.

So, that study had a lot more richness in it than, in fact, just that issue. But if we fast forward, then, how we would do that study today, which I think is what we need to think about, 1960, in order to measure a chloramphenicol level, you needed 25 ml of blood. Well, you know, think about the circulating volume in a baby. You couldn't have really done pharmacokinetics back then.

Today, we would have done a non-therapeutic single dose pharmacokinetic study to figure out what the right dose of chloramphenicol was in the first place, and then if we engaged in a clinical trial--and we will talk about it later

--we would have used data safety monitoring boards because we are starting off with unknown therapy in a very complex setting. It would have been a very different kind of study.

In fact, when I see that study sort of getting, if you will, bad press, to me, it is a paradigm of what could have been done in the 1960s, but also points out just how much progress we have made in trying to do these kinds of studies today, in fact, back then, I think with the ethical decisions, probably might have gone to a placebo-controlled trial even in that setting.

Just one more anecdote. I was involved in one placebo-controlled trial, something that should have been obvious and safe. It was a study of Vitamin C in cystinosis. Somebody had shown in vitro quite clearly that ascorbic acid decreased the cysteine content of fibroblasts from these children. Everybody said it's unethical to do a placebo-controlled study because, after all, Vitamin C is safe, we weren't going for megadoses of Vitamin C.

With the data safety monitoring board, with the placebo-controlled study, the study was stopped because the children on Vitamin C were going into renal failure faster than those on placebo for reasons we don't understand, but again that tells us we need to be in awe of biology and medicine.

DR. CHESNEY: Dr. Kauffman.

DR. KAUFFMAN: Just to follow up on Dr. Spielberg. I have a question for Dr. Temple and then a comment.

You emphasized throughout your talk the efficacy side of the coin and the importance of placebo or controlled studies for efficacy. To what extent are placebo controls or some type of control important for safety evaluations?

DR. TEMPLE: To assess the rate of some event, you need either an active control whose rate you are pretty sure of, or once again, a placebo. If you don't, the fact is many of the so-called safety studies in pediatrics are just open trials, and the only choice you have is to attribute everything bad that happens to the drug, which may not be the right conclusion. It is hard to think of what the alternative is.

Sometimes the desire is to show that a particular drug lacks a side effect that another drug has. In that case, all of the same kinds of thinking applies. That is a study with a hypothesis is, as a general matter, failure to show a difference is uninformative unless you know that the control would have had that effect.

For example, if you wanted to show that Claritin or something like that is non-sedating in children, you really do need a sedating antihistamine to compare it with and show a difference. If nobody gets sedated, that just might mean that that was not a sleepy population. So, the

same kind of thinking.

DR. KAUFFMAN: Or kids don't get sleepy.

DR. TEMPLE: Or kids don't get sleepy at all, right, so it may not be an advantage. Once again, you need the positive control in that case, the drug that causes sedation serves as your placebo. It's the internal standard.

DR. KAUFFMAN: I wanted to follow up on the widespread off-label use that Steve referred to in the chloramphenicol study, because that has bothered me for a long time and I am not alone, I don't think.

That is, it is fairly common in pediatric medicine that a drug is adopted into widespread off-label use across the pediatric age group, becomes accepted in the pediatric practice community sort of as, quote, "the standard of care," but it is off label, and then we come along and say we need a study.

What are the ethical implications of taking an accepted, non-FDA-approved, non-labeled, but accepted treatment and then trying to enroll kids into a formal placebo-controlled study or some other type of controlled study to evaluate that drug after it has come into widespread use? There are just dozens of examples of that in pediatric medicine. It's a practical issue, too.

DR. TEMPLE: And it is a formidable problem. One

possibility is the randomized withdrawal study. For example, if you think drug whatever is an effective antidepressant, not that depression studies in children have been very successful for the most part, but if they did, you could take people who are being treated with whatever the antidepressant people think the standard is, and then randomized to a new antidepressant or placebo, with the early escape provision being that as soon as depression rears its head, the children would be out of the study, they would escape.

That isn't exactly what you wanted to know as far as the treatment of acute depression goes, but it would give you some indication that the drug is active in that setting. Whether that is sufficiently more comfortable to allow people to engage in that study is something that I am not fit to answer, but people here probably can.

DR. CHESNEY: I think we could take one more burning question and then we need to move on.

Dr. Spielberg.

DR. SPIELBERG: Just a good example of that situation, Ralph, that sounds trivial, but it really had a big effect on pediatric practice, was a placebo-controlled study of what we were all doing back when in treating otitis, which was to use pseudoephedrine and antihistamine combinations.

A placebo-controlled trial was done which showed that, in fact, those drugs really did not help, and that was tremendously important because in practical practice, we were always telling parents you have to go home and you have to give this drug plus the antibiotic. There were therapeutic and compliance issues associated with that.

The practice was dramatically changed overnight when those studies came out and people no longer were writing for those products. So, even though it was standard of care and everybody knows that, in fact, it turned out to be wrong, and practice changed as a result of it.

DR. CHESNEY: Thank you. That reminds me of the mist tents in cystic fibrosis.

I think we need to move on. Our next speaker is Dr. Charles Weijer, who is a bioethicist and Assistant Professor of Medicine at Dalhousie University in Nova Scotia, and he is going to talk about the ethical concerns in pediatric placebo-controlled trials.

Ethical Concerns in Pediatric Placebo-Controlled Trials

DR. WEIJER: Thank you very much.

[Slide.]

I have been interested in the issue of the ethics of placebo controls and the ethics of randomized controlled trials for some time. I trained at McGill University with my mentor, Benjamin Freedman, whom some of you may know as

really one of the founding figures in the ethics of randomized controlled trials. So, some of the ideas and criticisms that I am going to talk about today are Benjie Freedman's work, and much of them represent work that we did in collaboration, and a small portion of it is my own.

I feel a bit uncomfortable up here actually. I was asked to give a talk on the ethics of placebo-controlled trials, and I see that Dr. Temple has already given us a lecture on the ethics of placebo-controlled trials.

Believing that there is value in diversity, and so on, I think you will find that some of my views of the ethics of clinical research are perhaps at variance with Dr. Temple's views.

Let me set a broader framework here in terms of how we actually think about the ethics of clinical research. One of the founding documents that we continue to rely on in research ethics is a document produced in the late seventies by the U.S. National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research.

Now, that pivotal commission in its Belmont Report set out three ethical principles that guide the conduct of research involving human subjects, and those principles are respect for persons' beneficence and justice. Respect for persons requires that we respect the autonomous choices of individuals. An important corollary, particularly in the

setting of pediatrics, is that it also requires that we protect those who are incapable of autonomous choice.

Beneficence is typically expressed in terms of two complementary rules, first, do no harm, second, maximize potential benefits while minimizing harms, and the principle of justice, of course, refers to the fact that there needs to be an equitable distribution of the potential harms and benefits in clinical research.

In the setting of pediatrics, I think a couple of aspects of this ethical framework require further exploration. First, the fact that the principle of respect for persons requires that we protect those who are incapable of autonomous choice.

I think that protection shifts appropriately our emphasis onto the principle of beneficence, in other words, what are acceptable benefits and risks to which children in research may be exposed.

Now, I have got a couple of overheads here before I switch over to Power Point, and this I think reflects, I hope, an evolving view internationally in the ethics of research with regard to the specific guidance that institutional review boards, local ethics committees are given with regard to how is it exactly that they determine in a particular study whether the risks and benefits in that study are acceptable.

Sometimes we talk about an acceptable risk-benefit ratio, other times we talk about an acceptable balance of potential benefits and risks. We need to recognize, of course, the metaphorical nature of each of those phrases and what IRBs need is specific guidance as to how exactly they are supposed to determine that.

What I want to present here is, in fact, work that I have done as a part of the World Health Organization, Council for International Organizations of Medical Sciences, that is, CIOMS, Steering Committee revising their 1993 international guidelines, and also work that I have just recently submitted to the U.S. National Bioethics Advisory Commission on philosophical aspects of risk analysis.

What we see here is really a comprehensive and systematic approach to the analysis of risks and benefits in research. It recognizes that many, many clinical studies contain a mixture of procedures. Some of those procedures are administered with therapeutic intent, others are not administered with therapeutic intent, that is, they are administered solely to answer the scientific question at stake.

The fundamental recognition of this ethical approach is to say that the ethics of therapeutic procedures need to be evaluated separately from the ethics of non-therapeutic procedures. Therapeutic procedures must pass

the test of clinical equipoise. This was the notion originated by Benjamin Freedman in a 1987 article in The New England Journal of Medicine that I think many recognize as setting the moral foundation for the modern randomized controlled trial.

Freedman said that in order for a trial to proceed ethically, at the start of the study there must exist a state of genuine uncertainty in the community of expert practitioners as to the preferred treatment.

So, then, an IRB reviewing a study must review the justification for the study, and may use things like a literature review or consultation with impartial experts to determine that, in fact, a state of clinical equipoise exists.

Now, this, in fact, is crucial to the determination of whether a placebo-controlled trial is ethically permissible or not, and I am going to go on and say a lot more about that.

Non-therapeutic procedures, on the other hand, offer by definition no prospect of benefit to research participants, and therefore, any appeal to a so-called risk-benefit calculus is inappropriate. There are no benefits to trial participants, period.

So, we need to use a different moral calculus. First off, risks must be minimized, so, for example, if one

could piggyback a procedure on something that is being done for therapeutic purposes, you need do that, and after one has done that, the risks must be reasonable in relation to the knowledge to be gained.

That fundamentally involves an assessment of the study's value and requires not only input from relevant experts, and so on, but also, in fact, requires the input of community representatives on institutional review boards, because ultimately, the benefit here is to the community or to our society at large.

Thus, with regard to the evaluation of non-therapeutic procedures, we are not talking about a risk-benefit calculus, rather, we are talking about a risk-knowledge calculus.

Now, that framework holds for all clinical research. It gets a little more complicated with children because, as I said, additional protections must be invoked because children are a vulnerable population.

[Slide.]

A lot of this is the same, and I want to just point out a couple of differences. The first difference, the first protection is that you can't do a study involving children unless, in fact, the institutional review board is convinced that the study hypothesis requires the inclusion of members of a vulnerable population, and, of course, in

the context of today, that is children.

One might add refinements to this, as I have noticed that this very committee has, with regard to the inclusion of older children who perhaps may be either capable of consent or at least capable of assent versus the inclusion of younger children who are incapable of either.

The second major protection actually applies only to non-therapeutic procedures, and that is, that the risks posed by non-therapeutic procedures can be no more than a minor increase above minimal risk.

There is a lot of misunderstanding about minimal risk and for good reason. Part of it is that the National Commission itself was sort of confused about what the concept should mean, but I think it has become quite clear that the minimal risk is only sensibly applied to non-therapeutic procedures.

So, then, this "no more than a minor increase above minimal risk" threshold means that a study may only proceed if there is no more than a minor increase above the risks of daily life for the study population in question.

As I have said, this only applies to non-therapeutic procedures. I can't say that enough. The whole confusion in this country over proper standards for emergency research emanated from a failure to recognize that very simple point. Fundamentally, it is a qualitative

judgment made by the institutional review board, the IRB acting in loco parentis, acting as the scrupulous parent would act in making such a decision.

I am now going to switch over to the Power Point.

[Slide.]

When we are talking about the permissibility of placebo controls, fundamentally, we are looking at a question that has troubled ethicists for probably a couple of decades now. That is, that we believe that physicians owe their patients certain duties. One of them is the duty to care, a duty to provide effective treatment to their patient.

Many physicians and ethicists in the eighties became very concerned as to whether it would be permissible at all for responsible clinicians to enroll their patients in randomized controlled trials, in other words, trials in which patients would receive one treatment or another, or one treatment and even placebo, as a matter of chance. "How," many asked, "could the ethical physician ever allow her patient to be allowed to be randomized to treatment?"

Well, there were a lot of attempts at answering that question, and I think there was only one good answer, and the answer I think is a very clever one, and it is, of course, clinical equipoise, and you see the definition there, I have already mentioned it, but let me tell you what

I think is actually really important and innovative about it.

Clinical equipoise actually recognizes that under certain circumstances, treatments within a randomized controlled trial can be potentially consistent with the standard of care to which clinicians are held in their practice.

Now those conditions are when there is a state of honest professional disagreement among expert clinicians as to the preferred treatment. So, then, equipoise recognizes that experimental treatments or other treatments within a randomized controlled trial may be consistent with the standard of care and therefore, and importantly, consistent with the physician's duty to her patient, and that is the reason why, under these constraints, doctors may ethically offer trial enrollment to their patients.

[Slide.]

Essentially, when one thinks about the choice of control treatment, this has implications for when one can permissibly use a placebo control. Let me give you just sort of a summary view of this.

Essentially, equipoise holds that for first generation treatments, in other words, when there is no available therapy, one ought to, in fact, use a placebo control, but for second generation treatments, certainly

after placebo-controlled trials have demonstrated a treatment to be effective for a particular patient population, for second generation treatment, the comparator must be an active control.

Now, Benjie Freedman, when sort of working out logically the implications of this, said there were five circumstances in which one may use ethically a placebo control. First off is there is no standard therapy. Second off, a standard therapy is no better than placebo. Third, a rather theoretical category, the standard therapy is placebo, not too common.

Importantly, if there is doubt regarding the net therapeutic advantage of standard therapy, now I don't know the exact circumstances of the chloramphenicol trial, but it seems to me that it is conceivable that the chloramphenicol trial, in fact, was perhaps done because there was rising doubt as to whether chloramphenicol was safe and effective. So, that is an example of that important condition.

Finally, when standard treatment is unavailable due to cost or short supply. This obviously touches on the HIV trials in Africa and Thailand, that whole debate, and I pray that we are not going to get into that here.

One other thing I might mention is that the question of no standard therapy also might apply to circumstances where no treatment is a part of standard

therapy, and so, for example, the otitis media study that we heard about where a substantial proportion of clinicians, in fact, would not advocate the use of antibiotics under certain circumstances might be a case in which we could do a placebo-controlled trial.

Now, Dr. Temple, in his lecture--and I do have to respond to this because Dr. Temple does like to talk about ethics, which is a good thing--but he comes up with a standard that he claims is well accepted.

It may be believed by many, but it is surely without any moral foundation, and that standard is that it is okay to do a placebo-controlled trial unless you are going to kill someone or disable them permanently.

Well, that seems to me to be problematic. Recall now that all of this comes from the physician's duty to her patient, the physician's duty of care to her patient. For Dr. Temple and others who believe this standard to actually provide a moral justification, to actually say that this is a philosophically sound notion would have to begin by arguing that, in fact, a physician's duty of care for her patient is only limited to circumstances in which the patient might die or be permanently disabled.

Now, if that troubles you, if you think that maybe that would be a bad thing for the practice of medicine, then, it follows as a matter of pure logic that you must

also be troubled by the standard that Dr. Temple has put forward.

[Slide.]

Let me add a couple of additional cases to Benjie Freedman's list. I think they are implicit, but let me just make them explicit.

I think it is similarly unproblematic to do trials on patients who are, in fact, refractory to standard treatment or standard second-line treatment or standard third-line treatment, what have you, and the reason is, is because for refractory patients, there is by definition no standard of care, right? So, it actually falls under the first of the five of Freedman's conditions.

[Slide.]

Another important example is that it is perfectly permissible to use a placebo control in add-on studies. Why? Because everybody gets the standard therapy, nobody is being deprived of any needed medical treatment, and so, in fact, it is permissible when everybody gets standard therapy, to do a comparison of the experimental treatment versus placebo.

[Slide.]

Now, this is an example of why people like me should never be given programs like Power Point, you know, because then we try and put graphs in and numbers. This is,

as I am sure you will agree, completely incomprehensible.

What I wanted to talk about for a few minutes here --and please ignore this slide--are what I think are some advantages of active control equivalent studies, because until about 1996 or so, when Benjie Freedman and myself published a two-part paper in the Journal of Law and Medicine and Ethics, in the fall '96 issue actually, really people were talking about placebo controls and their miraculous advantages as if the only alternative was to do bad research, to do sloppy research, to do unfortunate things like take a standard superiority trial, and if there is no difference between the two treatments, fallaciously conclude that they are equivalent.

Well, of course, that is bad science, and really nobody has seriously suggested otherwise. What we suggested, however, is that there are, in fact, rigorous trial designs called an active control equivalence study out of respect for the originators of the trial design, and that, in fact, in circumstances, many circumstances in the regulation of drugs, it seems to address the questions that we want to get to.

Ultimately, a placebo control is only going to provide us with information as to whether a new treatment is better than nothing. Well, it seems to me that in our society, a society of rising costs, the multiplication of

me-too drugs, and so on, that, in fact, perhaps we might want to know whether the new treatment is as good as what we are using now.

I think there are some real advantages of this trial design, the so-called active control equivalence study. Dr. Temple has described it to you quite accurately I think, and really what it asks is, is there strong evidence that this new treatment is no worse than a certain percentage, no more than a certain percentage worse than the current treatment. So, is it no more than, say, 10 percent worse than, and if we have strong evidence of that, then, we will conclude that the treatments are equivalent.

If one actually wanted to do an active control superiority study, the studies would need to be huge for sure. Here, I have one example, you know, assuming certain placebo effects, standard drug effects, new drug effects, and so on, and you can see that the active control study would, in fact, be something like 14 times larger than the placebo-controlled study.

But, in fact, an active control equivalence study surely is larger than a placebo-controlled study, perhaps one and a half times as large, two and a half times as large. It depends very much how you define equivalence.

But the point is, is that sample size requirements are actually intermediate between the placebo control and

the active control superiority study, and I think that largely makes it feasible.

So, that is the point of this slide. There is only one word that this slide should actually have on it, and it should just say "feasible." I will change that.

[Slide.]

I think there are scientific and clinical advantages to active control equivalence studies. I think that so-called Ace studies ask questions that are actually clinically relevant. Now, the FDA, under the 1962 Kefauver-Harris Act, as I understand it, is actually only able to require that new drugs have some effect.

So, in fact, the actions of the FDA may be somewhat limited by the provisions of that Act. Well, that isn't necessarily what clinicians want to know, and that isn't necessarily what patients want to know. It seems to me that the standard, is this treatment better than nothing, is inadequate. Better than nothing is just not good enough.

An Ace study asks I think the question that clinicians and patients want to know, that is, is this treatment as good as or better than what we are currently using.

[Slide.]

There are other scientific advantages. We talked earlier about the use of Claritin, non-sedating

antihistamines. Well, you know, in fact, an active control equivalence study helps us ask exactly that question. We could say are they roughly equivalent, and furthermore, a superiority question, does it have less side effects. So, there is the possibility of incorporating multiple hypotheses into this trial design.

[Slide.]

Well, I think there are regulatory advantages, too. I think we have to worry about the fact that a regulatory agency may approve a drug that is superior to placebo, but, in fact, that does not rule out the possibility that the drug is substantially inferior to standard treatment, and it seems to me if the purpose of a regulatory agency is to protect the public in some way, that we need evidence that new treatments are, in fact, at least equivalent to old treatments.

There is also the issue of cost, why is it that new drugs never seem to be cheaper than the old ones. Well, as you are discovering here in the United States, and as we are discovering in Canada, in fact, we can't afford everything, and some concerns about the cost of new treatments need to be incorporated into studies.

This was noted by Henry and Hill in the BMJ a few years ago, who said many new drugs are expensive, and in some countries, drug budgets are growing faster than other

health care sectors. The key questions are: how much better are the new drugs than the old ones, how much more does it cost to obtain additional benefits, and does the extra cost represent value for the money.

Well, I think those are important questions, and I think, as a society, we need to address them.

[Slide.]

There are also ethical and legal advantages. I have said a lot about this, but let me put it yet another way, an advantage of an active control equivalence study is that patients are not knowingly given inferior treatment, and that fundamentally is what is at stake.

That is what the Declaration of Helsinki--you noticed I haven't mentioned that document--but that is what it really means in that sort of confused wording of Article 2.3, is that the medical care of patients ought not be disadvantaged by trial participation.

That is what it means. I have avoided appealing to it. I think it has been a mistake in the debate to appeal to it too much because it's a badly written document, but as I have tried to argue, research ethics and everything that we have been doing in research ethics for the last 30 years, in fact, argues to the same conclusion.

I think doctors, institutions, institutional review boards, and who knows, maybe even regulators, ought

to be worried about the liability of enrolling patients in placebo-controlled trials when effective standard treatment exists.

As I have said, doctors owe a duty of care to their patients, and an investigator's chief concern ought to be the health and well-being of her patient, not her own career, not, you know, sort of the consulting fees that she gets from the drug company, not making the FDA happy, but the health and well-being of her patient.

Providing a placebo when standard effective care exists may, in fact, be negligent practice and may be the basis of a lawsuit.

[Slide.]

So, what we have tried to get here are a couple of questions - placebo-controlled trials, are they ethical, are they necessary? I think the answer we have gotten to is sort of a qualified no to both questions. Surely, placebo-controlled trials may be accepted in carefully defined circumstances.

I have talked about add-on treatments, treatment-resistant patients, where there isn't a standard of care, and so on, but I think the active control equivalence study design is underutilized, and I have tried to outline how, in fact, there are some scientific, clinical, regulatory, ethical, and legal advantages to that design.

Thank you.

DR. CHESNEY: Thank you very much, Dr. Weijer.

Our next speaker is Professor Francis Crawley, who is Chairman of the Ethics Working Party for the European Forum for Good Clinical Practice, and a member of the Ethics Working Group for the Confederation of European Specialists in Pediatrics.

He is going to be speaking to us about ethical concerns in pediatric placebo-controlled trials from the European perspective.

Ethical Concerns in Pediatric Placebo-Controlled Trials from the European Experience

PROF. CRAWLEY: Thank you, Madam Chair.

Ladies and gentlemen, it is really a great privilege and an honor for me to have a few minutes to address you on the European experience with respect to pediatric controlled trials.

I want to thank Drs. Jayne Peterson and Elaine Esber for helping to facilitate my presence here and also for helping me to understand the conversation that you have been having as a committee, the ongoing conversation you have been having with respect to the ethics and the science of clinical trials in the pediatric population.

I also think that I should thank Dr. Robert Temple for, although we haven't communicated on this particular

meeting, he has been very helpful to me personally in understanding the relationships between the U.S. and Europe and in a wider sense, as well, through much of his participation in the discussion.

I think it really is a great honor to be here to be able to speak to this committee. What you people in this committee will decide will affect not only children in the United States, but it will affect directly children in Europe, and I can tell you from my experience with the WHO and UN-AIDS and CIOMS, it will affect children directly in the world at large. Your openness to have persons such as myself and Dr. van Zwieten-Boot to be able to come and talk about our experience will help this.

I think also there will be a reciprocal relationship, as well, and that is the way in which we decide in Europe to conduct clinical trials in the pediatric population will also affect to some extent the way pediatric trials are carried out in the United States.

Dr. van Zwieten-Boot presented you with what I think is an excellent map of the regulatory framework for clinical trials in Europe, a very complex and difficult mapping. As she pointed out, I am somewhat outside of that map, and the map I wanted to introduce you to, just in a wider sense perhaps, another map of Europe, has to do perhaps with health and the situation of health in Europe.

I want to point out to you that it was not until 1992 that the European Union received a mandate in public health, that mandate described in the Treaty of Maastricht, and it is reiterated and described somewhat differently in the Treaty of Amsterdam.

This is a limited, very limited area for the European Union to act in the area of health. Most of the actions in the area of public health are reserved for the member states, and that affects clinical trials directly, and I think Dr. van Zwieten-Boot showed that quite well here.

[Slide.]

Also, Europe is not only the 15 member states to the European Union, as you all know. There are 41 member states of the Council of Europe, and all of these member states feel themselves to be European, and are, from a European's point of view, European.

So, Europe is a wide concept and a complex and difficult concept. Within the concept of Europe, there is a wide expression of different feelings about culture and how culture influences decisions that are made in the important areas of our lives, and one area, of course, is health.

I can tell you on Saturday I attended a meeting in Belgium of specialists in radiation where there were speakers who came from England to present a particular point

of view on managing radiation practice, and one could feel a strong difference between a U.K. approach and a Belgian approach to rather simple matters in care and common practice.

As. Dr. van Zwieten-Boot pointed out, at the European level, one is very hesitant to talk about ethics outside of cultural context. There are good reasons for that. But nevertheless, both within the regulatory framework, as Dr. van Zwieten-Boot pointed out, and also outside of that framework, there is a wide discussion today going on now, an increasing discussion on the role of clinical trials in pediatric medicine, and that is what I want to look at with you.

I have given you some handouts, but I have also, in the presentation itself, I have reduced the number of slides I will speak to, and I will try to speak most directly now to the issue of the placebo-controlled trial in pediatrics.

[Slide.]

This slide you don't have in your collection. It is the only slide you don't have. I have tried to summarize somehow by using some concepts here. I think that the pediatrician's concern in practice, the physician's concern in practice has to do with the duty of care and the standard of care, and decisions based on these two ethical and

deontological requirements.

The duty of care is clearly an ethical requirement, indeed, it is a requirement we all have in all areas of our life, but it is also requirement specific with respect to health that the physician has, and that is expressed in the Physician's Oath.

The standard of care is an expression, in a certain sense, of a generalizable way of caring for patients in particular circumstances, and this standard of care is usually put forward by the profession itself, and is a deontological standard.

Both the duty of care and the standard of care are generalizable concepts that speak to a generalized population, but the physician or the pediatrician is concerned in an ethical sense in the first place with the person who is standing in front of him or her, and that means you are concerned with an individual in treatment, and here, we can speak of the bonus pater familias here, the responsibility the physician has to decide in a specific circumstance using generalizable concepts and generalized background from the duty of care and the standard of care.

[Slide.]

Ronald Kurz, Professor Kurz from the University of Graz in Austria is the Chairman of the Confederation of European Specialists in Pediatrics, the Working Party on

Ethics. He was formerly, until this year, he was also President of CESP.

He recently expressed that, "It is in the interest of children to evaluate medicinal products with scientifically proven methods. A precondition is minimizing distress and risk due to studies."

I think that what we can say in a generalizable sense today for the European experience would be the following two things: One, there is a need to examine clinical trials in pediatrics. There is a need to do them. I think there is a greater awareness of a need for it, of the deficiency in pediatric medicine without having those trials, and a concern with how to carry them out. That is one thing to say.

A second thing to say, as Professor Kurz here indicates quite clearly, is I find in the European discussion, I think in almost any country I go to within the terms here, is that there is a strong interest in protecting the child, but not only protecting the child, but in finding out what the interests and the concerns of the trial are, and allowing those interests and concerns to be articulated within the circumstances of treatment, which in a clinical trial sense would be in the circumstances of experimentation.

That is an interest to assure that the voice of

the child is heard, and that at any age.

[Slide.]

Professor Peter De Deyn from the University of Antwerpen recently wrote that, "Properly controlled randomized controlled trials form the only scientifically valid tools."

In his writing here, he reflects a very strong European position, and I think an international position today, since 1948 with the British Medical Association, the British Medical Journal, the expression of the randomized controlled trial as the founding or as the way of justifying, giving us evidence for one treatment versus another treatment.

[Slide.]

He goes further, Professor De Deyn, he insists, and I quote, "It is ethically justified that the optimal, and therefore often placebo-controlled and ethically founded, randomized controlled trial meets the duties of benefiting society and increasing knowledge"--and then here I think somewhat less sophisticated than Dr. Temple--"and without jeopardizing the well-being of the experimental subjects."

[Slide.]

The justification for randomization is scientific equipoise or equipoise in general, and we can look at this

as both scientific equipoise and personal equipoise, and we can take this back to the earliest writings on randomized controlled trials in 1948 in the BMJ.

[Slide.]

Scientific equipoise insists that the medical community is genuinely uncertain as to which treatment is best.

[Slide.]

Personal equipoise, that the patient himself/herself is in a situation, as well, of uncertainty as to which treatment is best. Sometimes personal equipoise also refers to the physician's own uncertainty, the investigator's own uncertainty here.

But also I think it is very important--and in terms of pediatric trials, this idea of personal equipoise is very important--because the justification for the invitation to the patient is not only a scientific justification here, but it is also a justification in the motivation for the patient to consent.

Of course, in the pediatric population, this becomes more complex.

[Slide.]

Drs. Wagner and Herrmann, they are both philosophers, trained in philosophy, Ph.D.'s in Philosophy. Dr. Wagner works for Solvay Pharmaceuticals in Germany. Dr.

Herrmann is a Professor of Bioethics at the University of Berlin.

In a recent article, they are wrote that, "Benefit and risk are ethical commodities determined normatively on the basis of empirically proven preparation characteristics occurring with a certain probability."

I have lifted this out of context. I think it speaks for itself out of context. In context, there is no undertone here, there is no problematic with this. For me, there is a problematic here. I think what they are saying is quite true. Benefits and risks are commodities that we are using in ethics in order to justify randomized controlled trials. We are using our weighing and assessment of benefit-risk as normative ethical tools for justifying randomized controlled trials. They are commodities.

[Slide.]

Again, there seems to be no awareness I think in the article of what is being said here. "For the management of uncertainty, ethical principles are important decision-/action-guiding tools."

If the randomized controlled trial is the Golden Rule, then, it is uncertainty that becomes the problematic for ethics in science, and here, both from an industry point of view, if you want, and from an academic point of view, it is the management of uncertainty that forms our key interest

in the design and carrying out of randomized controlled trials.

[Slide.]

So, a question.

[Slide.]

Are placebos and controls ever justified in pediatric research? The answer is clearly yes. Both are permissible in some circumstances. Where their use is justified in adults, the same may be true in children, subject to consent.

[Slide.]

Are placebos and controls ever justified in pediatric research? The answer is clearly no. New treatments should always be tested against old and there is no case for withholding established treatments from children even if the evidence for efficacy is thin. Furthermore, placebos mean deception and controls signify uncertainty of a kind--uncertainty again--of a kind to which children should not be exposed. This was published by Professor Tim Chambers from Ireland just recently this year. This is the seventh question of the seven questions.

[Slide.]

Conclusion. Pediatric placebo-controlled trials can only be justified when the design, enrollment, and conduct of such trials are such that they are in the best

interest of the child-participant with a view towards his/her health and a concern with his/her dignity.

Thank you very much.

DR. CHESNEY: Thank you, Dr. Crawley, for clarifying the seventh question of the seven questions. I think with the permission of the Executive Secretary, that we will take a 10-minute break now and then come back with questions before we hear from Dr. Ellenberg.

If you could be sure to be back in 10 minutes, please, we will proceed.

[Break.]

DR. CHESNEY: The questions that we are being asked to address, which are in the handout that was on the table this morning, are slightly modified from the ones that we received at home, so please be sure to use the ones that are in the forms that were on the table.

Now we have 10 minutes for questions from the subcommittee for Drs. Weijer and Dr. Crawley.

Yes, Dr. Danford.

Questions from the Subcommittee

DR. DANFORD: I would like to ask Dr. Weijer in particular about two potential criticisms I see with the concept of clinical equipoise that he cites as a principle on which the ethical clinical investigation is based.

It seems to me that this might be a somewhat murky

standard and a somewhat inappropriate one, murky in that it doesn't really give us a threshold to go by of what represents actual genuine clinical uncertainty, and inappropriate in that we have numerous examples where the standard of care and the opinion of experts hasn't really stood up to the harsh light of scientific scrutiny.

Could he address those two issues and see if he can support the concept of clinical equipoise a little bit better?

DR. CHESNEY: Dr. Weijer, did you hear the question?

DR. DANFORD: I can ask it more briefly. Is clinical equipoise too murky a concept for actual use in that we don't have a threshold to tell us what represents genuine uncertainty, and is it too inappropriate a standard in that the standard of care and the opinions of experts are so often wrong when they are held up in the harsh light of scientific research?

DR. WEIJER: Thanks for that question. Hopefully, all the other banquet rooms will hear my answer, too. It's only just.

[Laughter.]

DR. WEIJER: No, I don't think--I think historically, one needs to recognize where the concept of clinical equipoise comes from, and I think that is why I

brought us back to the question which people seem to forget, and it was a burning question 20 years ago. The question is, can an ethical physician ever offer trial enrollment to a patient under her care.

I think the innovation of equipoise is to recognize that experimental treatments or other treatment arms within a randomized controlled trial may be consistent with standard of care, and therefore, offering trial enrollment may be consistent with the ethical and legal duties of the physician.

Clinical equipoise is certainly no more murky than the notion of standard of care, which is the legal and ethical norm that governs the practice of physicians. I don't believe it suffers from any fault or any more murkiness than the notion of standard of care. Standard of care with perhaps its flaws successfully governs the practice of physicians, so therefore, I think clinical equipoise with its certain amount of murkiness admittedly is an adequate standard for clinical research.

Fundamentally, you know, you might ask, well, what is genuine uncertainty, and there being all kinds of really silly studies published, you know, saying what percentage of physicians, is it 50 percent have to think this new treatment is a good idea, or 49, or what have you, and I think that fundamentally misconstrues the question.

What it is in an ethical standard meant to guide the deliberations of IRBs, and the point of the matter is, is that they need to take reasonable steps to assure that a state of clinical equipoise exists, and that often involves looking at the study justification, consulting with experts, looking at the literature. In practice, it is a concept that I, many other ethicists, and many IRBs utilize, and I think successfully so.

DR. CHESNEY: Dr. Fost.

DR. FOST: Well, I don't think the problem is that it is murky, I just think it's the wrong standard. That is, the assumption that the community standard, that the standard of practice or the community equipoise, as you call it, is safe or effective is just wrong in the absence of science.

The examples are too numerous to count, and the number of children who have been killed and harmed by that assumption is in the hundreds of thousands. Let me just mention a handful from your own city.

Dr. Usher from Montreal for 10 or 15 years had every newborn in North America with hyaline membrane disease with RDS being treated with concentrated solutions of bicarbonate to correct the respiratory acidosis. This was standard practice. It was universal practice.

Jerry O'Dell was the sole person screaming in the

wilderness that this made no physiologic sense, that his studies in mice showed that it made no sense, but it wasn't until his disciple, Mike Simmons, did the randomized placebo-controlled trial showing that it was causing more harm than help, that these concentrated solutions were shrinking the brain and causing intracranial bleeding, and was one of the major causes of brain damage in newborns, and it is no longer done today. Nobody does it. But for 10 or 15 years, it was, and untold thousands of children were killed and harmed by it.

Oxygen, the unregulated use of oxygen for nearly half a century, it was standard of care, and the assumption, it must be safe, you know, it's everywhere, and the notion that oxygen had a dose response curve and that there was a right dose to use and a wrong dose just didn't occur to anybody, again until a single person began showing, Arnold Pace, that it could be harmful.

The whole basis of genetic screening and newborn screening programs in North America, now in the world, the PKU study, it was just assumed that everybody with a high phenylalanine had PKU and had to be on a restricted diet. It was the standard of practice throughout the country, it wasn't just the standard, it was mandated by law. What could make something more the standard? It just didn't occur to anybody for a decade that phenylalanine restriction

could make you retarded, and second, that a high blood phenylalanine didn't mean that you were at risk for PKU. In fact, 90 percent of children in retrospect were not at risk.

Exchange transfusion for minimally elevated bilirubin in normal newborns. I could identify studies that cumulatively have killed hundreds of thousands of children based on an assumption that the community standard was the right standard.

So, it seems to me a better standard is individual equipoise, that is, the investigator, himself or herself, has to have reason to doubt. The notion that the American Academy of Pediatrics says this is a great treatment is, to me, not sufficient.

The question is whether there is any science behind it, and the investigator must persuade somebody that there is not any science behind it and that it is worth studying.

The second point I just wanted to disagree with you on is this notion, your statement--if I have it right--that the hypothesis must require using a vulnerable population. That seems to me wrong also, that is, for children who have life-threatening illnesses, such as cancer, for which there is no other effective treatment.

The hypothesis that a new chemotherapeutic requires study in children is not true. It is just that it

may very well be in the interests of children to be in such a study. Rabies would be another example. If there were an effective anti-rabies drug, the hypothesis of showing that this agent is effective against rabies wouldn't require studying it in children, but if you had a child with rabies, you would surely want him or her to be in the study if there was appropriate animal work, and so on.

Thank you.

DR. WEIJER: May I respond?

DR. CHESNEY: Yes.

DR. WEIJER: Thank you.

DR. CHESNEY: I was going to ask you how much it was worth to you.

DR. WEIJER: Well, with respect, Dr. Fost, I think listening to your comments, one would have to wonder why anyone goes to a doctor. You make it sound as if every standard treatment is not only ineffective, but harmful, and surely that is unlikely to be the case.

I think you have misread my talk on a number of levels, and I am only going to have time to address a few of them. Most importantly, I am not from Montreal, I am from Halifax, the proud home of Dalhousie University, and am no longer at McGill. My university requires me to point that out.

Second of all, I am not advocating for a concept

which you call "community equipoise." That is a confused notion coined by John Lantos and Jason Karlowisch in the literature. It is not one that is widely advocated. I think I was rather clear in advocating for a notion called "clinical equipoise," advocated by Benjamin Freedman in The New England Journal in 1987.

I think you also misunderstand the fact that I am not arguing against good science. I think medicine is where it's at today fundamentally because it's undergoing a shift from an art based largely on idiosyncratic ideas and case stories to one that is based on a foundation of good science. I wholeheartedly support that.

Clinical equipoise, in fact, is the ethical notion that allows randomized controlled trials to go forward in medicine.

The examples you raised, I think are really unproblematic for clinical equipoise. You speak of them as if, you know, science couldn't go forward somehow if we believed in this notion of clinical equipoise. As I think I showed quite clearly in my list, there are numerous circumstances. Science can always go forward. The question is, is how is it best to go forward ethically and scientifically.

A placebo-controlled trial, as I said quite clearly, is indicated when there is a growing doubt as to

the efficacy of an existing treatment, and therefore, clinical equipoise would have supported the trials you pointed to with regard to the treatment of RDS in neonates, the treatment of hyperoxygenation, and so on.

So, Dr. Fost, those trials would have gone forward under the notion of clinical equipoise.

I guess there is so much more I would like to respond to, but just let me say one last thing, that with regard to my requirement that the study hypothesis requires the inclusion of the vulnerable population, again, you misconstrue me.

The study hypothesis, for example, in a chemotherapy trial involving children is not is this chemotherapy agent in the abstract effective and therefore we could just test it in adults, but rather, is it effective in the treatment of this particular childhood cancer, and that, of course, would be sufficient, you know, ceteris paribus, to justify the inclusion of children in that study.

I am sure we will have more to say to one another later.

DR. CHESNEY: Thank you.

One more question. Dr. Nelson has been indicating he had one for some time now, and then we will move on.

DR. NELSON: Charles, you may want to stay at the mike because I am interested in your reaction to this

interpretation, moving in a slightly different direction.

I find myself compelled and have learned a lot in reading about the issue of assay sensitivity and the need for an internal control within a trial to be able to determine that.

My question is this. If one of the conditions under which you need such an internal trial is where there is a diverse population of variable response, there is sort of difficulty in predicting whether a population would respond to treatment that is proven effective. Let's limit it to those circumstances.

Could one bring that down to the specific patient-clinician encounter where one would then be uncertain if that individual before you would have a spontaneous resolution, would respond to the drug or wouldn't, not to where the uncertainty in that clinical encounter could be a justification for recommending to that patient consistent with one's obligation that you enroll in a trial that has an internal standard even in the presence of a proven effective agent?

DR. WEIJER: Thanks for that question. It reminded me that there was something else I wanted to say to Dr. Fost.

This notion of individual equipoise, I think more properly referred to as "Peto's uncertainty principle," is

an idea that a lot of people find appealing. Certainly if you are British, I believe you are bound to swear allegiance to it. Certainly in North America, it is a notion that is beginning to take hold.

Basically, it says, you know, it is ethical for a trial to proceed so long as the individual doctor is uncertain in her own mind as to the preferred treatment for a particular patient, essentially your question I take it.

It is I think a deeply problematic notion, and in the next couple of week I have got an article coming out in the British Medical Journal actually criticizing the notion of the uncertainty principle in favor of clinical equipoise.

The problem with just resting everything on the uncertainty of the individual clinician is multiple. First off, and I think most fundamentally, it fails to recognize that the norms to which we hold clinicians are not individual norms, but rather community norms.

They are governed by the norm of the standard of practice of the community of expert clinicians. There are good reasons why we don't allow individual doctors to be guided by whatever beliefs happen to be in their head simply because doctors, just like everyone else, can hold crazy beliefs or incompetent beliefs, and the sort of standard that the uncertainty principle articulates would offer no grounds upon which to find those actions problematic.

The second problem with that kind of thinking is that it doesn't allow randomized controlled trials to be conducted in a very important circumstance, namely, where everybody is certain.

Now, that may sound curious to you, but, in fact, there are all kinds of circumstances where everybody is sure they know what to do. They just all disagree with one another.

Take, for example, a trial, a very important trial in the early seventies, NSABP BL-6, the conservative breast management versus mastectomy trial, which it essentially addressed the question of, for the treatment of early breast cancer, do we need to engage in fairly radical surgery or can we use breast-conserving surgery followed by radiation therapy.

Well, surgeons are a pretty certain lot overall, and in fact, there were such strong feelings in these two camps that the trial had a tremendous amount of difficulty getting off the ground. Well, according to this notion of individual uncertainty, individual equipoise as we have heard it called, or I think more properly Peto's uncertainty principle, those important trials, when there are essentially two entrenched camps each advocating their own treatment, could not ethically proceed.

Of course, according to clinical equipoise, which

recognizes community disagreement, those important trials would be allowed to go forward.

DR. CHESNEY: Thank you very much. Interesting point.

Dr. Susan Ellenberg will speak with us next. She is the Director of the Office of Biostatistics and Epidemiology for the FDA, and she is going to address a very important issue, which is are data safety monitoring boards necessary for every pediatric trial or under what circumstances might they be useful.

Use of Data and Safety Monitoring Boards and their Role in Pediatric Clinical Trials

[Slide.]

DR. ELLENBERG: I thought we should start with a definition. A data monitoring committee--this is my definition, other people may have different definitions, pretty straightforward--is a group of experts that reviews the ongoing conduct of a clinical trial to ensure continuing patient safety as well as the continuing validity and scientific merit of the trial.

[Slide.]

These committees go by a variety of names. I am using the phrase data monitoring committee because that has been the phrase adopted in the International Conference of Harmonization documents. You will frequently hear these

called data and safety monitoring boards.

I think you can take as many as you want from Column A and one from Column B and one from Column C, and you will probably find some committee somewhere that has been called by that name. So, I didn't want anybody to be confused as to whether a data monitoring committee is something different from what they are used to having it called.

[Slide.]

Why do we need to do interim monitoring of trial data? I am not sure if I need to even address this question given the chloramphenicol example that was presented earlier, but there are a number of reasons actually that go beyond that.

First, we want to identify rapidly any safety problem, and that is important for interim monitoring whether or not there is a data monitoring committee. You have got to watch and make sure there is nothing unexpected that was happening that would make you reconsider whether the trial should continue.

You need to look at the data to identify any logistical problems with trial conduct that you might be able to correct, and therefore, have a better quality trial by the time you get finished - is the accrual inadequate, is there undesirable distribution of baseline characteristics.

Maybe something was wrong with the randomization program. Are there too many dropouts and too much noncompliance, and some intervention may be needed to make the trial worthwhile.

We want to evaluate the continued feasibility of the trial as presently designed. If some of these problems can't really be fixed, it may not be worth continuing the trial, and perhaps we should go on to something else, and finally, and what gets the most press, to determine whether the trial objectives have already been met and the trial may be terminated early. That is, the results are sufficiently definitive that we don't need to go on to the end.

[Slide.]

Why data monitoring committees? Because everything that I have said doesn't mean that you need to have some kind of external committee. The people who are doing the trial could pay attention to all those things.

A data monitoring committee I think is needed for two main reasons. One, to ensure that there will be regular and systematic interim monitoring. We all know in our practice of our daily lives that there are certain things that we know that we should be doing, but we put them off, we don't pay as much attention to it as perhaps we should.

When you have a committee that is meeting on a regular basis, those data are going to be looked at, and

they are going to be assessed, and that is important.

Secondly, to provide an objective and a statistically valid assessment of the interim data. This is probably the major motivation for developing data monitoring committees in the first place.

[Slide.]

I am going to say a little bit about statistically valid because there are some complications here. Assurance of ongoing patient safety requires regular review and assessment of the accumulating data, but if we continue to do statistical tests each time we look at the data, we will increase our false positive rate.

If we define our statistical criteria, so that there is only 1 chance in 20 that we would have a result this extreme, if there were really no difference, and if you do that test 5 or 10 or 20 times during the course of the trial, the chance is much higher than 5 percent that you will eventually see that p less than 0.05, and you will have totally misled yourself as to the strength of the evidence.

So, once that was recognized, I think in the sixties and seventies there started to be publications about this, recognize that the strategy of just watch the data as it goes along and stop as soon as the p is less than 0.05 is inadequate.

[Slide.]

The most common approach used in clinical trials is something called group sequential testing. Instead of looking at the data as it comes in, you agree that you are going to look at it every 6 months, every 3 months, every year, whatever seems appropriate to the trial, the analyses are performed at pre-specified intervals and a statistical plan, a statistical monitoring plan is developed that provides boundaries showing what p-values might be required for early termination.

That would be consistent with having an overall false positive rate as low as the one we want, and those p-values usually vary with time. That is, you need a much stronger strength of evidence to stop early in the study, and as you get close to the end of the study, the p-values are more closer to the nominal 0.05, but the overall Type 1 error for the study is controlled at 0.05, and there are actually numerous ways to do this that I am not going to get into.

[Slide.]

No matter how fancy a statistical procedure you have, you can never get away from the need for judgment. It is not a question of pushing a button and seeing whether you are across the statistical boundaries. These considerations alone are inadequate for monitoring.

The algorithms that are developed, which I think

have been very, very useful in clinical trials, cannot account for all possible developments, and the exercise of clinical judgment is essential to the monitoring practice.

For one thing, your p-value is usually based on a single outcome variable, your primary outcome variable. There is a balancing of safety and efficacy outcomes that is absolutely essential. If you are across the boundary for efficacy, but some unexpected safety problem has arisen, that has to be balanced against the emerging efficacy outcomes. It may not be so clear that the study should be stopped yet.

There needs to be consideration of unexpected outcomes, as well as consideration of new information external to the trial. Another related trial finishes somewhere else and has been published, and that may have an impact on whether or not this study should be continued.

[Slide.]

Just a brief history of the data monitoring committees in the U.S. They have traditionally been used primarily for trials with mortality or major morbidity endpoints. In those trials, there is an ethical imperative to monitor efficacy, as well as safety. In fact, you can't even distinguish efficacy and safety if you have a major endpoint because if there is inferiority with regard to the efficacy endpoint, it is a safety concern.

Also, in these kinds of trials, the objectivity is seen as extremely important. It becomes much more difficult when you are looking at mortality outcomes or other very serious outcomes.

There is just a tendency to not want to let things get too much out of hand and having to balance that with wanting to make sure that you have a scientific result that people can believe and that will be persuasive becomes difficult. So, it is good to have an objective view, people who aren't formally involved in the trial.

Data monitoring committees have been components of many NIH-sponsored trials since at least the early 1960s. In fact, in the U.S., that is where data monitoring committees got started. They were rarely used in industry trials prior to 1990, I think because for the most part, industry trials didn't focus on mortality and major endpoints early, but with the increasing number of industry-sponsored trials with major endpoints, there is an increasing interest in use of data monitoring committees in other than government-sponsored trials.

[Slide.]

So, on to the important question of what trials need data monitoring committees. One answer is not all trials needs data monitoring committees. I think that we would get ourselves into a situation of doing more harm than

good if we required all trials to have data monitoring committees, but some trials would clearly benefit.

[Slide.]

Trials that might be stopped early for efficacy. Generally, it is very good to have a data monitoring committee, and for the most part, these are trials where the treatment is aimed at reducing mortality or morbidity.

If you are looking at a treatment to relieve a relatively mild symptom, even if you had a super blockbuster effect early on, you would probably want to continue the trial at the end because you would want to have a full safety database with a comparison to the placebo.

You would want to understand everything about possible safety concerns because what this treatment does may be useful, but it is not that critical to people's basic health. So, that is when you need a committee to look at those efficacy results and the stopping boundaries carefully.

So, in these kinds of trials, there is an ethical requirement to terminate a clearly inferior treatment, which there would not be necessarily in a less serious situation, and there is a need to ensure that the kind of statistically valid approach that I mentioned before is used for decisions about early termination or we want to control the false positive rate.

[Slide.]

We might sometimes want to stop a trial early for lack of efficacy, and an example might be a treatment aimed at controlling symptoms of a chronic disease where you need long-term observation. People are going to be treated for a long time. The endpoint might not be mortality or irreversible morbidity, but it might be something that has a strong relationship to quality of life.

When it becomes clear that the new treatment is clearly inferior in some way, you might want to terminate the trial, and so that the trial participants could revert to a standard treatment.

Now, here, the false positive issue is not relevant. You are not going to make a decision that a new treatment is effective or that you are going to possibly prove an ineffective treatment. What is at issue is the power, whether you are going to stop too early and perhaps not identify a potentially effective treatment.

[Slide.]

Some trials other than these that raise special safety or ethical concerns sometimes might benefit from a data monitoring committee. Trials of novel and potentially dangerous therapies. We have all been very aware of the recent issues in gene therapy, and there have been calls for data monitoring committees for early stage Phase I gene

therapy trials.

Xenotransplantation is another area that has been very controversial, using animal tissue transplanted into humans with possibilities of transmission of infections, and so you might want to have an outside objective committee looking carefully at the safety data from such trials.

I can tell you from personal experience that all of the Phase I, the initial Phase I HIV vaccine trials all had data monitoring committees. They were also randomized and placebo controlled. Special issues arising, you may want an outside committee.

Trials with informed consent waived. This is the only type of trial that the FDA requires have an independent data monitoring committee. Trials of a new treatment in an emergency situation, the patient is unconscious or otherwise unable to provide consent, and there is no proxy, no family member or legally authorized representative readily available, and there is a provision in our regulations that such studies can be carried out without a patient's consent, and these studies have lots of extra protections required for them including an independent data monitoring committee.

[Slide.]

There are certainly some special issues in pediatric studies that may increase the desire or usefulness of a data monitoring committee. You have got a vulnerable

population obviously. Consent is always by proxy, and with assent needed for children over a certain age. We are always more concerned about issues in vulnerable populations.

Long-term effects are especially important in pediatric studies, issues of physical growth and cognitive development, so there are a lot of things that we are concerned about, safety of treatments, and a variety of things that we want to watch and perhaps might want an independent committee not vested in the trial to be looking at those and helping with those decisions.

A possibly relevant issue is that products investigated in children may be available if they are already approved for use in adults, so the issue of when do you stop the study and make a treatment available to people who want to use it isn't quite the same as it often is in adult studies, because these, for better or for worse, these treatments are available to be used in children off label. So, that is a little bit of a different situation.

Finally, I don't think that there can be any argument that there is an extra emotional component in treating sick children, and it is often useful to have again a separate, independent committee helping to make objective judgments.

As has been pointed out, there might be a tendency

to want to stop a study if one treatment looks somewhat better than the other, perhaps before it is definitive, and it is not going to help children if there is ineffective treatments on the market, and so those judgments can be very difficult.

[Slide.]

Now, I am going to talk a little bit about the nuts and bolts of data monitoring committees. What kind of people do you have on data monitoring committees? This is a list of sorts of people that were mentioned in NIH trial data monitoring committees at a conference that I participated in some years ago - clinical medicine and the appropriate specialty or specialties related to the trial, biostatistics and biomedical ethics were the three areas of expertise most commonly mentioned although in trials you would sometimes find people expert in the basic science/pharmacology, epidemiology, clinical trial methodology, law, and increasingly patient advocates or community representatives instead of, or in addition to, somebody with special expertise in biomedical ethics.

The size of data monitoring committees, however, may be as small as three, so you obviously aren't going to have necessarily all of those expertise on every trial.

[Slide.]

I would like to say a little bit about an

independent data monitoring committee. It's a phrase that I have used. An independent data monitoring committee--and again this is my own definition--is one in which no member has either any personal basis for preferring the outcome to be in one or the other direction.

When I say "personal basis," I mean a personal gain. Obviously, everybody would like to have a new treatment be developed that is going to be better to treat children, so in that sense, everybody may have a preference, but I am talking about a personal preference, and I will go on to that in the next slide, or any ability to influence the trial conduct in a role other than that of DMC member, that is, that you wouldn't want the knowledge of the accumulating data to influence how the trial was carried out.

[Slide.]

So, the types of conflicts of interest that could lead people to have personal preferences, one, clearly financial involvement either with the product being studied or with a competing product, patient involvement, those entering patients on the study, treating study patients or evaluating patient outcomes could be influenced, perhaps not consciously, but could be influenced if they know which treatment is which, and that would be particularly the case for studies that are unblinded.

There is also the issue of intellectual involvement, the person, somebody who prepared the protocol or who was involved in earlier development of the product, somebody whose intellectual standing in the community may stand to be greatly enhanced if this turns out to be a big blockbuster product, that may reduce somebody's objectivity.

I think regulatory involvement is an issue here, as well. I think those of us who wear regulatory hats and have to make decisions later on may not want to be involved in making other kinds of decisions during the course of the trial.

[Slide.]

Interim results of clinical trials monitored by committees should be held confidential. I think that is the way this mostly works. The knowledge of interim data could affect the trial conduct, and that is the bottom line reason. It could affect how patients are entered, how many or what kind. It could affect how patients are cared for and whether or not they are encouraged to stay on the protocol or not.

It could affect how patients are assessed, that is, those evaluating the outcomes, and it could certainly affect an action that a sponsor might take to decide on their own that the study should continue or to be stopped, and having an independent committee being the only group

that is looking at the interim results improves the ability to maintain this confidentiality and therefore protects the integrity of the trial.

[Slide.]

Data monitoring committees have been given a variety of responsibilities. I think it is important to recognize that what data monitoring committees do has only recently been widely on the table. A colleague of mine, Janet Wittes, wrote what has been a widely cited paper called, "Behind Closed Doors," about data monitoring committees.

They have different approaches and different structures have been developed at a lot of different places, and so they don't all run the same way, and I think we are in very much of a learning stage about data monitoring committees and how they work, and perhaps how they should work.

Almost all data monitoring committees are involved in evaluating the accumulating data with regard to efficacy and safety. That's the bread and butter. They may recommend termination or continuation of the study or they may recommend other study modifications either to improve the conduct of the trial or to improve safety. For example, they may feel that the dose level needs to be reduced. There is a concern about the level of toxicity that is being

observed.

Some data monitoring committees are asked to review and approve the study protocol. They are asked to play a larger role in assessing study conduct, and they may recommend additional analyses if the analyses that the statistical center presents to them, they feel they are not getting all the information that they need to make their decisions.

[Slide.]

Regulatory status. As I mentioned, there is only one mention of data monitoring committees regulations in the U.S., and that is that they are required for the emergency research studies in which informed consent has been waived.

They are mentioned in several guidance documents. The ones that have been developed by the International Committees for Conduct of Clinical Trials, the Good Clinical Practices. The E-6 guideline mentions that use of data monitoring committees. E-9 guidelines, statistical principles for clinical trials goes into a little more detail, not a whole lot, about data monitoring committees.

[Slide.]

I will just read to you the brief statement in the E-6. The sponsor may consider establishing an independent data monitoring committee to assess the progress of a clinical trial including the safety data and the critical

efficacy endpoints at intervals, and to recommend to the sponsor whether to continue, modify, or stop a trial.

The independent data monitoring committee should have written operating procedures and maintain records of all its meetings, and that is all that is stated. So, there hasn't been a lot of guidance from the regulatory standpoint anyway about operation of data monitoring committees.

[Slide.]

I would just like to conclude with a mention of the Office of Inspector General Report on Institutional Review Boards that came out in June of 1998. Despite the fact that it was focusing on IRBs, there were a couple of recommendations about data monitoring committees.

One was that data monitoring committees be required for trials under NIH, OPRR, and FDA purview that meet specified conditions. It didn't say what those should be. It said we should figure that out. We need to define those conditions, and we all should specify requirements for data monitoring committee composition.

The second recommendation was that data monitoring committees should have primary responsibility for reviewing and evaluating the adverse experiences occurring in trials, and that these assessments, along with summary data, could be shared with institutional review boards.

Now, there is a working group at FDA that has been

looking at these recommendations. I should update this. We are not considering development of a guidance document. We are developing a guidance document, but it is a difficult task because, as I said, there isn't a consistent worldwide view of those these committees should operate and especially what is the best way for data monitoring committees to interface with IRBs, but we are working on this, and hope to have some guidance shortly, which I am sure will be controversial.

Thank you.

DR. CHESNEY: Thank you, Dr. Ellenberg.

Any questions for Dr. Ellenberg? Yes, Dr. Fost.

Questions from the Subcommittee

DR. FOST: Susan, could you say a little bit more on this issue? You have written about it elsewhere, I know, but your own view on the role of the monitoring committee prior to the formulation of the study, the study design, and stopping points.

As you pointed out elsewhere, it is very difficult to be a member of one of these things and be ethically responsible when you are in stark disagreement with the design or with the consent form or with the stopping rules. But when you are ask, as a condition for being on these things, to be involved in that, the sponsor or the investigator says it slows everything down, you are

micromanaging something that we have spent two years developing with a lot of experts, we don't need your help on that, that is not why we are asking you, but that you are being asked to serve over a project that you sort of feel uncomfortable about.

DR. ELLENBERG: I think you are exactly right, and, you know, I don't need to repeat what you have said, but my own feeling is that if you can't, if you are asked to be a member of data monitoring committee, and the protocol is one especially with regard to what the monitoring guidelines are and what would be the conditions under which one might stop the study, and so on, and so forth, if you do not feel that that is appropriate, and is going to give either a valid answer or is going to adequately protect the safety of the people on the trial, those are the two reasons for the committee, then, I don't see how one can serve on such a committee.

I think the only solution is to not be on the committee.

DR. FOST: It is not a trivial point about the name of the thing then. If you believe that the committee, or whatever you call it, should play some role prior to the initiation of the study, then, get the word data out of there. I think it should just be called a monitoring committee or an oversight committee, because if your

recommendation leads to them being called data anything, somebody will say--they usually do--look, we are a data monitoring committee, we are not a design committee, we are not a consent committee.

DR. ELLENBERG: I will tell you what happens when you just say monitoring committee. People get that confused with site monitoring and other kinds of monitoring. Some people say monitoring, some people say auditing. No matter what you do, there are going to be some people who are going to figure out a way to interpret it in a way that you don't want.

So, I am not so worried about the words, but I think that in most cases, the data monitoring committee does get a chance to get a look at the protocol beforehand. I agree with you that there is often reluctance, but, you know, it is the same with IRBs. An IRB looks at the protocol, and they can decide--and people get irritated with them, too--but, you know, when you have oversight, you are going to irritate people.

DR. CHESNEY: Dr. Nelson.

DR. NELSON: The question relates around the issue of objectivity and the sharing of data from monitoring committees to IRBs and to participants. My understanding of one of the reasons data monitoring committees were formed initially was to prevent investigators from looking at trend

data and deciding to walk with their feet and abandon various trials.

The question I have is the extent to which investigators, clinicians and participants would want to know probability data about which arm they are in that is not reaching a so-called objective p equals less than 0.05, which is just a statistical definition of objectivity.

How does that square with IRB's obligation to report results or information that affects the participants willingness to participate? So, for example, if I am in an arm that has a 95 percent probability of reaching p equals less than 0.05, the study may not stop, but I might consider that relevant to my willingness to continue.

DR. ELLENBERG: Well, what you are raising is sort of a fundamental conundrum of randomized trials and one that many people have wrung their hands over for many years, and some folks have written that it is actually unethical to keep all these results confidential, and the results should always be out and available, and people should be able to make these decisions.

I think it is recognized that if that were the case, we would never be able to complete clinical trials, and I think that, you know, I can see that Dr. Fost is raising his hand, and he is much more familiar with the bioethics literature than I have, but I think that there is

a better answer to that than I would be able to give, so, Norman.

DR. FOST: Just quickly. I think the solution to that, Skip, is the consent form--they haven't to date--and they need to say there will be analysis of this data during the trial that will not be available to the investigator or to you. It may show significance, and we are simply not going to tell you that. If you don't like that, then, don't be in the study, but a condition of being in this study is we are going to withhold data unless an independent committee says it's time to stop.

DR. CHESNEY: Thank you.

I am sorry we have to move on because we are behind and we have to start the session this afternoon at 3 o'clock because it's a totally separate session, and we have new speakers coming in.

Our deadline now is that we have to break for lunch at 12:15, so, Dr. Murphy is going to give us general comments about the case studies, and then Dr. Birenbaum will give us Example A, and we will have 15 minutes or so to discuss that first question.

Subcommittee Discussion of Case Studies

Introductory Remarks

DR. MURPHY: For the committee, I wanted you to please note that the questions are slightly different from

the ones that were mailed to you. We have eliminated the example that was not a real life case, so the ones that are on the table are the ones that we will be discussing today.

We have put before you three levels of cases or examples of trials that we thought were progressing from the least controversial to the more controversial, and we will stop at the end of each set of examples and present questions to you.

The medical officers who were involved and working in selecting the examples and developing the questions will present them to you. We have tried, in response to the committee's requests last time, to provide more details, and yet develop some commonality amongst the cases that we are not talking about so specific that we can't apply some broader principles to these.

We reviewed quite a binderful of cases in trying to develop the commonalities in the case and then have them be slightly different, so that we could pose or focus the questions for you.

We look forward to your discussion. The categories are the add-on studies, which is a drug or placebo are added to an established therapy on which the patient has relapses or less than optimal control of disease.

What we are calling the classical placebo-

controlled trial, basically, that is a placebo-controlled trial where there is no approved pediatric therapy. Approved adult therapies may have failed in prior pediatric studies. That will be the second category.

The third category of trials will be withdrawal trials, which will be randomized withdrawal studies possibly with early escape features that decrease the duration of exposure to a therapy that is ineffective for a given patient.

Dr. Birenbaum, if you would come on up and present the first set of examples.

Example A: Pediatric Placebo-Controlled Add-on Clinical Trial Design

[Slide.]

DR. BIRENBAUM: As Dr. Murphy said, the placebo-controlled add-on trial design examples for discussion today are actually taken from pediatric studies submitted to the agency for review. We have tried to provide enough detail in the description of these studies for the committee to focus its subsequent discussion and the questions that follow are to provide an opportunity for the committee to comment on both the ethical issues specific to each study, as well as the trial design in general.

In our first example, asthma, children with the condition were stable but with less than optimal control of

signs, symptoms, and/or exacerbations.

After fulfilling the enrollment criteria, patients received standard of care plus study drug or standard of care plus placebo. Standard of care included continued maintenance of prior pharmacologic therapies, such as short-acting beta agonists and additional asthma controller medications.

Specific trial design elements in this study included several hundred 2- to 5-year-old children with a history of asthma who were enrolled at multiple centers. A two-week, single-blind standard of care plus placebo run-in period, which assessed randomization eligibility and patient compliance.

A 12-week, double-blind randomized active treatment period in which patients received either study drug plus standard of care or placebo for standard of care. The protocol further specified a 36-week open label extension period to determine safety and tolerability, an action plan for worsening symptoms in individual patients.

Criteria for individual patient discontinuation from treatment, and a blinded interim analysis that assessed and compared adverse events and exacerbation frequency of asthma. I should point out this was not a data monitoring board.

Safety measurements included adverse event and

asthma exacerbation monitoring, physical exam, vital signs, routine labs, and twice daily peak flow monitoring. The efficacy parameters included daytime and nighttime asthma symptoms.

[Slide.]

In our second example, seizures, children with the condition are stable, but have less than optimal control of the seizure events. After fulfilling enrollment criteria, the patients were randomized to receive either standard of care plus study drug or standard of care plus placebo.

They will have continued maintenance of ongoing pharmacologic therapies, and additional child designed elements in this study included or will include 50, 3- to 12-year-old children with partial seizures, a 6-week baseline period with patients on standard of care to assess randomization eligibility and compliance, followed by a 12-week double-blind, randomized placebo-controlled trial in which patients received either study drug plus standard of care or placebo plus standard of care.

The protocol further provides criteria for individual patient discontinuation from treatment and standard measures of clinical and laboratory safety parameters. The primary efficacy parameter in this study is a reduction in frequency of partial seizures.

These two trials are examples of studies in which

the Food and Drug Administration is comfortable using this clinical trial design. It is less clear whether trials of this design necessarily warrant use of a data safety monitoring board or data monitoring committee.

Further, differences in the clinical implications of disease exacerbations may be different across the spectrum of medical illnesses, for example, an asthma exacerbation versus a seizure event.

We ask that you consider these issues in your discussion of the following questions:

[Slide.]

Is there a situation, population, disease or condition where this type of placebo-controlled study would not be appropriate?

DR. CHESNEY: Why don't you read through all three questions and then we will allot a certain amount of time for each one.

[Slide.]

DR. BIRENBAUM: What role, if any, does a data safety monitoring board play, is it necessary for the ethical conduct for each of these trials? Does having stopping rules for individual patients affect this decision?

[Slide.]

What are the differences in level of morbidity or discomfort in children that would recommend use of a data

safety monitoring board?

DR. CHESNEY: Thank you very much.

So, our first question: Is there a situation, population, disease or condition where this type of add-on placebo-controlled study would not be appropriate?

Yes.

DR. WILFOND: Well, I think the question would focus on why is it the case that optimal therapy isn't working, in other words, is it because they have been receiving a range of therapies, are people perhaps not having access to standard therapy or the best therapy. Perhaps they live in an area where they don't get access to good medical care.

I think that would be a reason where I think we might be very concerned about offering a clinical trial rather than the ideal therapy. It strikes me that one solution would be to have a list of standardized approach saying what treatments a person ought to be on before it is concluded that they have not responded to optimal therapy.

DR. CHESNEY: Thank you.

DR. WOLFF: I wasn't sure whether the discussion should be limited to these questions. There are some prior questions which I don't understand.

Why is safety and efficacy measured after the fact instead of before? In fact, in all four of these, it

somehow comes in the middle, and there is no prior Phase I or Phase II.

Another question is why does this protocol specify several hundred children instead of a specified number, so you could do some estimation. Maybe these are not relevant to your question, but they would certain be of concern to anybody who does an IRB review of these.

DR. CHESNEY: Dr. Murphy, do you want to comment?

DR. MURPHY: I think that again, the level of specificity could get us down to a very individual case, and we were making the assumptions that in this situation, you would have nothing in the Phase I or II trials that would modify your behavior in response to this question. So, if it is not there, we didn't put it there because we made that assumption.

Secondly, we did round the numbers. We tried to take actual cases again because you would have made these statistical assessments on whatever you thought the difference would be, and so we didn't want to get into making that difference. We thought we would prefer the discussion to focus more on if there were a class or if there were some broad category of safety or some other issue besides the calculation of the difference.

DR. WOLFF: But this first one in particular, both of them actually, specify that the safety and efficacy will

be done in the course of the study. Am I misunderstanding?

DR. MURPHY: Basically, the conduct of the trial is to look at the performance of this therapy for both its safety and its efficacy. You have set the trial up to look at that issue.

DR. TEMPLE: Maybe the question has to do with the definitions of what the trials of various phases do. It is common to describe Phase I studies as assessing safety. Well, that is sort of true, but they assess the safety of a single dose, which is not the full-bore assessment of safety that you are looking for. So, they do get you a little bit. They tell you that it is tolerated and nothing terrible happens.

What a Phase II study means in this context is a little hard to say. The first controlled trial studying effectiveness is either a Phase II or a Phase III study, it is sort of a matter of definition.

Whether this kind of trial should precede the sort of exposure safety trial that is common in pediatric settings could be debated. This gives you a better quality of information than just exposing a couple hundred people, but you are not going to carry out a very long-term placebo-controlled trial, so you don't really have too much choice.

Sometimes an active control trial if there was something you could study can get you safety, but I think

the thinking is this would be a relatively early trial before you know a great deal. Of course, you know everything in adults, which is relevant.

DR. WOLFF: I will shut up in a minute, but is the idea to save some time?

DR. TEMPLE: You mean by studying safety and effectiveness at the same time?

DR. WOLFF: Yes.

DR. TEMPLE: Well, see, I would say you always do that in a placebo-controlled trial. You are looking for the rate of--depending on its size--you are looking at the rate of relatively common adverse events, and you have a control to see any difference between, even in an add-on study, too, the difference between the group that gets the new drug and the group that doesn't on safety endpoints are presumably side effects that are due to the drug.

You learn that, and you also learn whether it works. I mean you always do that.

DR. MURPHY: I guess we would say that you shouldn't put any product into a child where you are not going to assess the safety aspects of it.

DR. CHESNEY: Dr. Gorman had a question.

DR. GORMAN: In response to Question 1, it seems to me that--and the discussions on the IRB on which I sit--always deals with the placebo controls and the amount of

safety for escaping people from studies with acute exacerbation of their diseases, and both asthma and seizures present good examples of those where the exacerbations can be immediately life-threatening or very rapidly life-threatening.

In these kinds of situations, placebo-controlled studies would be acceptable to our IRB as long as that safety was a little bit more aggressively assured than in this protocol where it says that AE's will be monitored, but no escaping is allowed or it is not discussed very dramatically in this protocol.

DR. MURPHY: Thank you. So, what you are saying is that basically, you just need clearly defined escape rules for the individual patient.

DR. GORMAN: Correct.

DR. CHESNEY: Dr. Nelson had a question.

DR. NELSON: It is actually on the open label extension portion of the asthma example. In other conditions, particularly some areas such as depression and psychological problems in a situation where there may be a possibility of a positive response to placebos or a spontaneous remission, our committees occasionally struggle with the fact that you could have someone on the initial randomized trial that is on the placebo arm doing just fine, and then is exposed to the drug unnecessarily.

We have tried to suggest, sometimes successfully, sometimes not, having the second phase not be just an open label, but to continue the blind and allow for perhaps crossover. If I recall, in reading, I think it was E-10 that might have even been the suggested model.

So, there are circumstances where the second open label phase presents some problems to those who are doing just fine on placebo.

DR. CHESNEY: Dr. Temple.

DR. TEMPLE: You could also, if you wanted to learn more about long-term effectiveness or maintenance, use both the responders on drug and conceivably the responders on placebo, enter them into a trial in which they are treated for a period and then randomly withdrawn with the potential for early stopping as soon as exacerbation occurs.

One of the things you always want to know is whether you have persistent effects. On the whole, nobody is prepared to do a six- or eight-month placebo-controlled trial in these settings. So, the randomized withdrawal with a standard for stopping therapy and crossing them over is perhaps one way to get at that.

There is also usually debate about how long to treat people, so it helps answer that question.

DR. MURPHY: Let me ask you. Dr. Temple just made a statement that nobody would do a six- to eight-month. Are

you suggesting, then, in the extension trial, that it would be appropriate to continue?

Certainly, the children, if you had clear stopping rules, would have been discontinued that you would prefer then that we have a randomized long-term extension as a possible alternative approach?

DR. NELSON: I guess the devil is in the details of what particular situation you are studying. My reaction to this particular protocol we reviewed last week was it wasn't clear to me why they didn't just design a six-month trial instead of do a six-week trial with a six-month extension.

As long as you are clear about who has responded well and have clear evidence of that, and have clear ways to respond to those who have responded poorly or are having difficulties, we were unclear why you couldn't just simply maintain the blind if indeed someone was doing just fine, and not start giving them a drug that they don't need if they are on placebo.

DR. CHESNEY: Dr. Murphy, some guidance. Shall we go on to Question 2 given only 10 minutes left?

DR. MURPHY: Two hands to your right. We would like to hear their comments.

DR. CHESNEY: So, we will stick with Question 1. Dr. Fink.

DR. FINK: Yes, I have a question. In this study, particularly with asthma, what happens when the standard of care involves the majority of study drugs? Many of us would define an inhaled steroid as a standard of care for asthma, at least moderate or severe, and yet, the majority of the studies are of inhaled steroids of various manufacturers, so that they usually exclude the use of an inhaled steroid to go into the placebo-controlled trial.

So, the exclusion criteria often take you out of the standard of care criteria.

DR. MURPHY: I think we try to get at that later on with the withdrawal, you have a population where the standard of care already is the steroid. What you are saying is that--and that is what we were trying to get at, what level of exacerbation--you are saying that one would say any child who is having exacerbations could not go into this trial because they would first need to go on to an inhaled steroid?

DR. FINK: Yes, the standard of care would say that that is actually the appropriate treatment, but then the study prohibits you from participating if you are already on the inhaled steroid.

DR. TEMPLE: If this is a case where you could conclude that an active control non-inferiority trial to added steroid was persuasive, and perhaps with steroids you

could, that might work and you might be able to do that kind of trial.

If it is a not so dramatically effective drug where you couldn't with any honesty assert that there is assay sensitivity, then that trial wouldn't be informative anymore and you would have to either abandon hope and forget about it or do the sort of thing that Dianne mentioned, we talked about later, do a randomized withdrawal trial, watching very closely for exacerbation, and you would have to decide whether you are comfortable with that design.

DR. FINK: Then, it would seem that it would lead to potentially the conclusion to your first question, that this type of study design would be inappropriate for any population where the standard of care included a drug of the class under study.

DR. TEMPLE: Actually, the definition of this case was where that hadn't been true. You are right, that is a very good question, but this case ducked that question.

DR. FUCHS: Hopefully answering one situation, then, I guess people would probably have problems with this study is if you are using IM as the method of delivery. I mean if you had to give a kid, not necessarily asthma, but seizures, you were all assuming it's either inhaler or by mouth. I think a lot of people would have problems if you are going to be telling someone they are getting a couple

shots a day, and it could be a placebo.

DR. MURPHY: So, you are saying where--again, trying to address the situation it would be unacceptable--where you have a standard of care that is less invasive and less distressful than the product which is more distressful to the child, is that your statement?

DR. FUCHS: That is how I would foresee it, and I would think that a lot of parents would see it that way, too.

DR. TEMPLE: I thought you were addressing the question of whether you should give an injection placebo.

DR. FUCHS: Well, that, too. I mean if you have a standard of care that is not an injection, obviously, and then you add another medicine, but the placebo is going to have to be the same method of delivery that your new medicine is, I think you would have a lot of problems with that. It could be the same for an I.V. medicine, too, you are just sort of taking it at a different phase.

DR. TEMPLE: You wouldn't object to one in which there was no treatment, though.

DR. FUCHS: No.

DR. TEMPLE: And then the question would be whether that is a credible study without a blind.

DR. CHESNEY: Dr. Wilfond.

DR. WILFOND: I have another issue related to the

issue of optimal control, which is not the question raised before, regarding the cause of the optimal control, but the concern that particularly in studies in pediatrics, you would at least potentially worry that the motivation of parents to enroll their child in the study was precisely because of the lack of optimal control, and I am just raising that as a question. This creates a tension that perhaps the motivation for participation would be based upon that concern, and you ought to at least make sure that there are ways of at least providing clear alternatives to the study in that regard.

DR. CHESNEY: Dr. Botkin.

DR. BOTKIN: I think this discussion highlights some of the difficulty about defining the standard of care, and I would say the issue is a little bit broader than what Dr. Fink had raised, and I would point to the antiseizure medication example and say if a patient were to enter the study with poorly controlled seizures on one seizure medication, is that person receiving the standard of care or not.

I would contend that by one definition, you might say that indeed they have since you are attempting to control those seizures. By another definition, you would say they hadn't since they hadn't progressed through what is a typical sequence of events, which is either increasing the

dose or adding additional agents, et cetera.

So, I think there is a risk with this type of justification, that patients who are inadequately treated are defined as being on the standard of care, and then justifying their inclusion in an add-on protocol.

DR. MURPHY: I would say that your point is well taken and we clearly would say that for this trial design, called an add-on trial design, the standard of care would be that which is acceptable in the community at that time.

The usual approach is that if a child is having seizures and they are not controlled with one anticonvulsant, that they would receive another one before they would be considered in any sort of control. Then, that would be two therapies that would be considered the standard of care.

Again, we didn't want to say two versus three for a specific disease, but try to get to the fact that there would be a defined standard of care.

DR. CHESNEY: Dr. Temple.

DR. TEMPLE: It is not uncommon in these trials to observe people on the supposed standard of care during the lead-in period. If they then fall below the level of control that was considered necessary for the trial, then, they wouldn't enter it. So, it gives you an opportunity to check for poor compliance and obtaining the optimal level,

and things like that.

I guess it seems worth noting that most of the drugs for epilepsy are not exactly pleasant, and have their own problems, so that you can imagine that people would decide on a standard of care that wasn't necessarily optimal seizure, but was some balance of seizure control and ability to tolerate it. But a lead-in period is the norm for these types of trials. Just take our word for it.

That is how they enter the screen, but then they would be looked at further usually. Dr. Katz is here and can tell me if I am right about that. There is often an observed lead-in period on whatever the supposed optimal standard control is.

DR. MURPHY: And that is why you see that in both of these.

DR. CHESNEY: Dr. O'Fallon.

DR. O'FALLON: No one has mentioned the fact that one of the limitations of this study design is that actually the question it is answering is whether this new therapy is effective in conjunction with the standard, whatever you choose it to be, and that really doesn't answer one of the questions you have been wanting, which is, is it effective, by itself even.

So that is a design limitation. It may be one that has to be accepted at the beginning, but we have all

seen therapies in which the timing and the order in which the therapies were delivered, two things can be effective when given one way, but not in the other way, and there are all those other issues that will never be sorted out with this particular design.

DR. CHESNEY: Dr. Ward.

DR. WARD: I just wondered if you would consider labeling this then for poorly controlled seizures as opposed to for seizures, because you have a very selected population to start with in which you are testing.

DR. CHESNEY: Dr. Kauffman.

DR. KAUFFMAN: I was going to make a related point, and that is it seems to me that one of the limitations of this approach is, particularly with the seizure example, is we intentionally selected a refractory group of patients, so there is a high probability of showing non-efficacy where the drug may really be efficacious in another setting or subpopulation.

DR. TEMPLE: All those last comments are absolutely right. The problem is that it is not easy to evaluate drugs in this setting. One proposal is, oh, just compare it with dilantin, but if you don't know what the seizure rate in the absence of therapy would be, you don't have any evidence that you have got any activity at all. You just don't know unless you let the person escape from

therapy.

So, this is a compromise, not an entirely satisfying one, that gets you at least some information on whether it works when you add it to the other therapy. Furthermore, you could say, well, that is the most important problem anyway, people who aren't being well treated by available therapy, that is the biggest problem.

How to get monotherapy is not well known. There are some careful withdrawal designs--Barbara van Zwieten can talk about those--and they are actually mentioned in the E-10 document, but how happy everybody is with those could be debated.

As long as it is considered bad to allow people to have more seizures than they otherwise would, and there is a pretty good case for that, this is a very thorny problem.

DR. CHESNEY: Dr. Hudak.

DR. HUDAK: I think one of the problems with this particular study design, too, that hasn't been explicitly recognized is the fact that this is, as Judith said, a test of standard versus standard plus new.

One has to realize that in that setting, depending what the agents are and what the biology is, there is always the potential that the standard plus new is worse than the standard, when, in fact, the standard versus new might show the new better than the standard when you are looking at

either safety or efficacy.

So, one has to step back and consider those issues in these trial designs, too.

DR. MURPHY: The other answer is that yes, we would be labeling it as Dr. Temple alluded to. We would not be labeling it for monotherapy, it would be labeled for adjunctive therapy.

DR. TEMPLE: There is one more problem that I should mention that you haven't yet. You can't really work up a drug that is similar pharmacologically to the drug you have already got this way, and that means that if it has a better side effect profile, you can't really discover it this way.

We see this on--just to divert for a second--in heart failure, the current therapies have to be given, you have to give everybody a diuretic, you have to give everybody an ACE inhibitor. Now you have to give them a beta blocker and pretty soon you will have to give them Aldactone.

So, all of the trials are add-on trials, but if somebody has a new ACE inhibitor, you can't study it that way unless you can come to the conclusion that an equivalence trial would be informative, which is a different question.

DR. CHESNEY: One last question, Dr. Spielberg, or

comment.

DR. SPIELBERG: I think all these comments are really right on the mark. The issue, though, in almost any drug development program is that it is iterative, and you get certain information from one trial that will lead to the next design for the next trial where you are confident that the drug in fact works and is tolerated reasonably well in a population. It is sufficient to go from a more severe population into a less severely affected population with a different trial design. It may be a comparative best model therapy.

But the issues again are really iterative ones and I suppose the question that Dianne is asking here is if this is an appropriate acceptable design to initiate a program for compounds like this.

DR. CHESNEY: I think we have to break now for lunch for just half an hour, please.

[Luncheon recess taken from 12:20 p.m. to 1:10 p.m.]

DR. CHESNEY: I think we are ready to begin.

Just two housekeeping issues before we start. The first one is that we do have to start our break at 2:45 because of the new topic to be discussed at 3 o'clock and new speakers. In order to do that, with Dr. Murphy's help, we have prioritized the remaining questions, so we will not

be doing all of them. Several of them can easily be handled together.

I think as the other examples are presented, you will see which questions we have decided to address and which ones we won't, and we will only address one more question for Example A, and that is the second one.

What role, if any, does a data safety monitoring board play, is it necessary for the ethical conduct for each of these trials? Does having stopping rules for the individual patient affect this decision?

Comments? Yes, Dr. Ward.

DR. WARD: Because the second therapy may alter the effectiveness of what is viewed as standard of care through either induction of its metabolism or inhibition of its metabolism, the previous level of control of the particular clinical symptoms may change dramatically, and having ongoing monitoring of that I think protects the patient in both of these clinical situations.

Even though I think we have chosen clinical situations, clinical conditions that we view as not life-threatening, they certainly can end up being almost life-threatening or leading at least to hospitalization. I think that needs to be detected in a timely fashion.

DR. CHESNEY: Dr. Fink.

DR. FINK: If we take these examples where both

studies are only 12 weeks in duration, I don't think it is practical to have a data safety monitoring board. By the time you actually could look at much data, the study will be terminated.

So, I think that where trials are under probably six months' duration, use of a monitoring committee probably isn't that practical.

DR. CHESNEY: Dr. Ellenberg, do you want to make any comment about that?

DR. ELLENBERG: I think part of it depends on--it may be only a 12 week course, but if it is going to take several years for the study to be completed, you might want to have somebody watching.

I think what I want to say most is that this kind of trial obviously needs careful clinical monitoring. The question about whether it needs a separate, independent group monitoring, looking over the shoulder of the people conducting the study is another issue. I don't think there is any question that it has to have monitoring, and a trial like that may, in fact, benefit from data monitoring committee, but you would need to tease out what are the special things about it that would require the separate, independent committee as opposed to having the usual people who are monitoring trials just taking care of it internally.

DR. CHESNEY: Dr. O'Fallon, do you want to comment

or did she say everything?

DR. O'FALLON: We do want to keep the length of time that the patients are on the study separate from the length of time it takes to do the study. That was my major reaction to what you have, but that other business up there about stopping rules for the patient and again the stopping rules from the study are two very distinct things, and I think we have got to keep them separate.

DR. CHESNEY: Dr. Fink.

DR. FINK: The other issue I think that comes up, and I think it could pose a risk with a data safety monitoring committee, at least with asthma there is a marked seasonality to it, and if you take the wintertime and you look at a new therapy, it is going to look highly ineffective or potentially worse than standard treatment because of the increased asthma exacerbations that occur every winter. So, seasonality is also going to play a role, at least in some of these disorders.

DR. MURPHY: So, what I have heard thus far is that in these two trials, which we have described for you and which we would have clear escape or stopping rules for the individual patient, and understanding that it is going to take longer than 12 weeks, but for this situation I heard one opinion that because this could affect the efficacy of your standard of care that you should have a DSMB, and the

other was that we do not need a DSMB.

Is that what you are saying or not? Again, what Susan said was what we are trying to point out. We would have very clear stopping rules for individuals in these trials.

DR. CHESNEY: Dr. Wilfond.

DR. WILFOND: What occurs to me is that I wonder if even with the stopping rules, if it was a case that suddenly almost every patient was being stopped very quickly, would that be the sort of information that would be a factor in a decision to continue the trial. If that was the case, that might be the role that a DSMB might play.

DR. MURPHY: So, there may be a role in these types of trials, particularly if you knew that there might be an issue with interactions or that that was a problem, or there is any other particular reason to think that there may be a worsening of the standard of care therapy particularly.

DR. FOST: Joan, there is a confusion here between escape guidelines and stopping rules. Any study like this would have escape guidelines or rescue guidelines is the word where any individual patient could stop on his or her own account, or their parents, or their doctor. Stopping guidelines have to do with an overall trend in the trial which shows that the drug is either toxic or unsafe or is not likely to produce a meaningful result.

Whether it is meaningful to have a DSMB for that reason depends on more information than I can glean from this, like how long the trial is going to continue and Dr. Fink's point about whether there is enough time to intervene.

DR. MURPHY: So, length of the trial.

DR. CHESNEY: Dr. Gorman.

DR. GORMAN: But even in a 6- to 12-week trial, enrollment could take place over several years, and the data, well, that is correct, for the individual patient it wouldn't make much difference, but for the trial management, and I guess what we all need reassurance about as we are sitting here trying to discuss this data safety monitoring board is how frequently the data is monitored in regards to how significant we think the effects will be, and I don't think we have enough data to really make that decision, and we all are on the side of caution or mostly all are.

DR. CHESNEY: Dr. Wolff.

DR. WOLFF: I think especially in the second case, where you really don't have a homogeneous group of partial seizures, and some of them are on any kind of medication where the addition may cause very serious effects, I don't see why there should be a question about a DSMB.

DR. CHESNEY: Dr. Spielberg.

DR. SPIELBERG: The other practical thing,

addressing what Dr. Ward brought up with respect to drug-drug interactions, in these kinds of trials, particularly with the anticonvulsants, many of which are inducers and inhibitors of drug metabolism, in addition to an external safety monitoring board, it is often helpful having an unblinded physician who is keeping track of drug levels of the other drugs.

In many of the trials we did in my academic years, in fact, we had to have somebody who was responsible for juggling the other medications to prevent other medications from getting into toxic ranges when a new drug was added on.

To the extent that you have to do that will be dependent on adult studies showing whether, in fact, these drugs are inducers or inhibitors, but if they are and they are likely to lead to drug-drug interactions, it is very important to have an unblinded member of the investigative team doing the adjustments of the other drugs.

DR. CHESNEY: Are you implying that there would need to be a DSMB for them to share that information or how does that relate to the DSMB?

DR. SPIELBERG: Not necessarily. It is usually a real clinical trial role, but it is another level of making sure of the safety of each individual subject in the study and making sure that none of those patients end up with unacceptable levels of the other drugs, either high or low,

because obviously, going down could exacerbate seizures, going up could lead to side effects.

DR. CHESNEY: Dr. O'Fallon.

DR. O'FALLON: I think the DSMB, its major value is with respect to the conduct of the study, and it does help the study team in the sense that they provide the objective look at the data. The study team can get pretty carried away or very much involved in a study, and that's okay, but then it helps to have the DSMB that is there to help to keep things in perspective.

Given that pediatric patients are so rare, I would think that almost every study of this magnitude that is done would end up being a bellwether study of some sort, and I think that we should consider that having to--well, the DSMB's ought to be part of the normal way of doing business in the pediatric research of these bellwether issues.

DR. CHESNEY: Dr. Kauffman.

DR. KAUFFMAN: I wanted to ask Dr. Murphy would these monitoring committees be required for a sponsor to appoint or would the FDA appoint them?

The reason I am asking is we have run over the last few years in the Pediatric Pharmacology Research Unit Network, repeatedly run into situations where a company was reluctant to place their studies within the network because they did not want to subject their proprietary information

to another overview group even accepting confidentiality. They just did not want to extend the exposure of their proprietary information.

DR. MURPHY: We would not be requiring them. There is not a regulation that says that we would require them. The reason we are having this discussion is that when we are designing trials, which we all frequently do, we ford the safety or efficacy issues, whatever they are, we may recommend to the company that they would be well served by having such a monitoring process in place, and we are trying to define the parameters in which our experts would also think that.

As far as their proprietary information, I think that the DSMB should be constructed, so that you would have people who would know that that is the type of information that they do not--let me back up.

People who would talk about what they discuss at a DSMB shouldn't be on a DSMB. I think, Susan, can you say it another way? Because it is more than their proprietary information that they can get out. If you were releasing information about the conduct of trials to the public, it can have tremendous impact in a number of ways.

DR. ELLENBERG: I think that is very correct. One of the issues, of course, is that up to this point there has been a relatively small number of trials that have had data

monitoring committees, and the people who serve on them are people who often have had that experience before and have some of this understanding.

That is one of the dangers of moving to a situation where suddenly there is 20 times as many data monitoring committees as we ever had, and perhaps not having all people who totally understand that.

I did want to comment, though, that another side of this confidentiality issue that we have dealt with is not so much that the companies don't want other people to see the data, but when you have an independent data monitoring committee, it is generally the case of the company itself does not have access to the interim data, because the recommendations for what should happen are then made by the data monitoring committee to the company, and that, in my experience, has caused much of the resistance of companies to establish them because they don't want to give up access themselves to the interim data.

DR. CHESNEY: Dr. Danford.

DR. DANFORD: I am inclined to agree that a DSMB would be very important for these studies, but I am nagged by one comment that Dr. Ellenberg made in her presentation to us earlier. She said that data monitoring boards are not always a good thing, and then she didn't say the reasons or the precise circumstances where they are not a good thing,

and I am wondering what she was thinking and whether it applies to either of these cases.

DR. ELLENBERG: I think it relates to what I was just saying. There are clearly some disadvantages to have a data monitoring committee. They add an extra layer of complexity to a trial. They add expense. They are complicated to develop and make sure that everybody is getting the information they need and when.

So, there is an extra layer of complexity that you can understand that people who are doing a trial don't necessarily want to have unless it is necessary. My concern now is if there are vastly more data monitoring committees put into place than we have had, there may not be enough people with the level of understanding of clinical trials. It is not just the clinical experience, it's understanding of clinical trials and how to interpret them, and all of that.

You don't want people advising you that know less about it than you do. So, a bad data monitoring committee is worse than no data monitoring committee. That is my concern.

DR. CHESNEY: I think that is a real concern. I was just asked to be chair of a DSMB, and I don't know anything about this particular drug or this protocol. It is going to take a lot of time on all of our parts, we are

inexperienced, and I am not sure that it is going to add much to anything.

But I wonder, Dr. Kauffman and Dr. Spielberg, if you could comment again on this issue, Dr. Kauffman particularly, since you do so many of these studies and you haven't had DSMB's presumably for most of them, under what circumstances do you think that we should absolutely recommend that there should be one?

DR. KAUFFMAN: I think, in general, where they would be of most value and be feasible or practical would be in the large Phase III studies that are going to be spread across multiple investigators and institutions, and ongoing for a prolonged period of time with a wide range of kids involved over a period of time, particularly for chronic conditions.

That is where I think they would have the most value. We do a fair number of short-term pharmacokinetic Phase I/II studies now, too, and for those, as Dr. Fink pointed out, they are frequently opened and done and finished and closed out before you could ever even convene a data safety monitoring committee, and to delay those four to six months to get them up and going, and so forth, I think would put such a blockade in this whole thing that it would just be counterproductive.

The other issue that was raised I think is very

important to think about, and that is, with the number of pediatric studies, the increase in the number of pediatric studies that we have seen and probably will continue in the coming years, to have a data monitoring safety committee for the majority of those, there aren't going to be enough people with enough time to do this.

It is just going to not be feasible to do it, so we are going to have to be selective and do it where it has the greatest impact on children's health, where there is the greatest potential risk, the larger studies, the greatest exposure to the pediatric population, I think that is where they have their greatest value.

DR. SPIELBERG: I would really agree with Ralph, and two other points. I think any situation where internally you are really concerned about early stopping either from a safety or an efficacy point of view, a drug for a life-threatening condition where you want to be able to make that drug more broadly available, as rapidly as possible, with all the appropriate stopping rules put in there, as well as where you are concerned about toxicity.

On the toxicity side, what Ralph said though is also a concern. Of the people listed on those committees, one thing left out is anybody really knowledgeable about pediatric AE's, and pediatric side effects of drugs and the ability to detect them and the ability to understand them is

really something of a specialty, and there are very few folks around who really can help out with those kinds of things. But if you are really concerned about side effect issues, you have to have clinical toxicology involved.

DR. CHESNEY: Dr. Murphy, do you think you have enough information that we should go on?

DR. MURPHY: Yes, I do, and I appreciate it because I think the issues that we hope would be brought out were, which is it would be very difficult to have the adequate type of DSMB that you would want for every single pediatric study. I think that we are trying to define the parameters, and we think that they definitely should be or one should at least consider the discussion that they should be utilized. So, thank you.

DR. CHESNEY: We will move on to Example B, and Dr. Rosemary Roberts is going to present that to us. She will tell us what questions we will address instead of all three.

Example B: Pediatric Placebo-Controlled Trial Design When There is No Approved Therapy

DR. ROBERTS: Good afternoon. All of the committee members and the invited speakers have in their packet, attached to the back of their agenda, the examples, and it might help if you just follow through and look at that while I read to you the essential elements of the case.

[Slide.]

For Example B, there are pediatric placebo-controlled trials where there is no approved therapy. Unlike the other examples from A and those that you will hear from C today, this is not a pediatric study that has been submitted to the agency for review.

Instead, this outline is taken from the written request template that the Division of Neuropharm has developed and is up on the web, so I am just going to go through the essential elements of the trial design that we are requesting.

Now, the assumptions for depression are that the patients have a chronic disease or condition that requires long term therapy. There is approved therapy in adults for the condition, however, there is no approved therapy in the pediatric population.

The trial design elements. Age range, it will involve children ages 7 to 11, and adolescents ages 12 to 17 with equal representation and a reasonable distribution across both sexes.

We are requesting two randomized, double-blind, parallel group, placebo-controlled acute treatment trials with a duration of 6 to 8 weeks.

One of the trials should be a fixed dose study including two or more fixed doses of the study drug as well

as placebo.

It is also recommended that there be a relapse prevention trial that would involve the randomization of responders from the acute treatment trials to continue on either study drug or placebo, with follow-up observation for relapse for 6 months or more.

The request also includes pharmacokinetic assessments that should be made in the relevant age groups and be able to adequately characterize the pharmacokinetics in those age groups.

The criteria for enrollment should include a valid and reliable diagnostic method for recruiting children and adolescents with major depressive disorder.

The study evaluations are to include a scale specific to pediatric depression and sensitive to the effects of drug treatment of pediatric depression, for example, the Children's Depression Ratings Scale-Revised, and a global measure, such as the Clinical Global Impression.

The study endpoints should be change from baseline to a single primary endpoint using the symptom rating scale chosen for the trial.

Routine safety assessments should be included.

In this example, there is no approved therapy in the pediatric population, but approved treatment for the

condition in adults is available. Further, it is believed that the efficacy in adults demonstrated in adequate and well-controlled trials cannot be extrapolated to the pediatric population.

For approval in the pediatric population, the FDA is requesting that efficacy be shown in two adequate and well-controlled trials of the placebo control design. For psychotropic drugs there is a concern that pharmacotherapy may have effects on cognitive development. We ask that you consider these issues in your discussion of the following question.

We are going to focus on Question No. 2. Recognizing there is a concern that psychotropic therapies may affect long-term cognitive development, what ethical issues arise when only information from short-term therapeutic trials is available?

DR. MURPHY: I would like to focus that even a little more, or expand it. What we are really getting at here is the question of duration of the studies. The information you have at the end of a study, which will be measured in months, in which you will be treating children, and what do we do about the long term, not just cognitive, but long-term studies.

DR. CHESNEY: Dr. Nelson.

DR. NELSON: I guess starting with a question,

what kind of control group would you propose to use for such a long-term study? I mean it would be worthwhile doing it, but I can't imagine you would want to have a 16-year placebo control.

DR. MURPHY: Well, that is the issue. What we are placing on the table is the fact that we do not know how one would have a controlled study in this situation, and what is the level of acceptability of having short-term data knowing that these products may be used on and off over the lifetime of the child, and when one does not have a way in which we feel we can design a controlled trial at this point.

DR. NELSON: I guess some information is better than none. Are we basically then trying to come up with a way to gather information in the absence of a control, or is there some way it could be controlled? I mean you have got the control guru to your left.

DR. TEMPLE: Well, it's a really hard problem. You sort of either accept population norms or do something like that, or you try to dream up a design. I have one I would throw out for comment.

It is probably not known how long you really need to treat people. One could compare two approaches to treatment, one in which you kept people on until a year had elapsed, which is probably not incompatible with some treatment, another in which you kept people on only for two

months after they had recovered and waited.

Now, both of those, I think would have to be considered within the scope of what standard therapy is, but comparing them might give you some idea about long-term effects, and you don't know the answer to which is better yet, so there might be some designs one could work on.

I don't believe a study like I described has ever been done, but it doesn't seem impossible.

DR. NELSON: I guess as a pediatrician, I have never thought of one year as a long time when you are looking at cognitive development.

DR. TEMPLE: No. At one year you stop the therapy and then if they recur, you treat again. The other is at two months you stop the therapy and if it recurs, you treat again. The assumption would be that you would have--well, I don't even know this--but you might have considerably more treatment and maybe a happier kid with the one-year therapy. The other, the shorter therapy might leave more episodes of depression, but might leave growth and development unimpeded. So, you might make the case that that is an interesting trial.

DR. CHESNEY: Could I ask a question? Can you do an adequate analysis of cognitive state in a child that is depressed? In other words, could you have a baseline that you could compare to a year later?

DR. MURPHY: I think what we are bringing out here are all the problems with this, is that you long-term-wise don't know what the normal outcome would be, and you may have a baseline that is actually worse, and so you are going to have an outcome in the long term that is better, and unless you have a control group that you didn't treat, which we don't think you could do, if you had made the diagnosis, the appropriate diagnosis, unless you have some other historical information, that would be very difficult, so we continue to hear the discussion because we are struggling with this issue.

DR. TEMPLE: But you might test cognitive function at a time when they weren't overly depressed. That certainly seems like a good thought.

DR. CHESNEY: I think Dr. Gorman was first.

DR. GORMAN: To go back to one of Dr. Nelson's previous points, the randomized withdrawal in studies like this presents some problems for our IRBs and may actually present an opportunity to answer your question at least on a moderately long-term basis if you use 6 months.

Rather than re-randomizing the responders in the acute phase of the study, knowing that some of the responders will be on placebo, continue to follow them without re-randomization in the follow-on course. Then, you can look at their cognitive skills in the active drug versus

the placebo in only the responders.

DR. CHESNEY: Dr. Spielberg.

DR. SPIELBERG: Just stepping back a little bit to the nature of the controls, because the first question that Dr. Roberts raised was that of non-approved therapy as a potential comparator rather than placebo, one of the things that we are going to face ubiquitously in pediatric studies that Dr. Temple didn't even address is that if you have non-approved therapies, you often don't have formulations.

If you don't have formulations, then, in order to do a controlled study of a non-approved therapy versus your new drug, not only don't you have a basis for doing it because the first drug is non-approved, but you also may not have a formulation that fits, which often leads into a double-dummy design, because you can't bind the formulations. They have different colors, they have different flavors, they may be bid, they may be tid, they may be qd. So, you end up with a very complex study design which often runs into major compliance problems, and in a situation with depression and such, you are going to be facing it even worse.

The other issue, though, is that--and we have faced this several times--is if there is no approved therapy, you can't even do a best available therapy approach.

You could fall back and say, well, what is community standard, but then you have to ask what is the scientific basis of that community standard, and typically, that will not meet FDA standards because the drug isn't labeled in the first place.

So, you are sort of chased around looking for a good comparator that is (a) non-approved, and (b) non-formulated, which makes from an FDA point of view a non-doable study, but also from a pragmatic point of view a non-doable study because you don't have the matched formulations available for a comparator. You can't keep the study blinded.

DR. MURPHY: Steven, this disease, we are talking about depression, you may not need a different formulation because of the age population.

DR. SPIELBERG: Although if you look at kids down to 7, fewer than 30 percent will be able to take pills depending on the size of the pill, and even at 11, only half the kids will be able to swallow pills, and if you look at those pills that are on the market in the OTC venue, which is the key to looking at what children can and can't take, the OTC preparations available for the 7- to 11-year olds are very, very tiny.

Very few of our Rx pharmaceuticals meet those criteria for friendliness for use, so that really does

become a problem, and compliance in depression obviously is a major issue, and if the kid has trouble swallowing it the first time, he is not going to take it the second time.

DR. MURPHY: Right. I am just saying it doesn't make it an impossible study because you may be able to find those kids who can take the preparation that you have.

DR. CHESNEY: Dr. Wolff.

DR. WOLFF: One of the concerns you raised was about whatever you mean by cognitive development and its long-term effects, is that--

DR. MURPHY: I really was expanding the question. It's just the long-term effects, cognitive being one of them, because these are CNS therapies.

DR. WOLFF: What I meant was that probably means something to do with the brain with these pills. At what point do you then make a determination that it does or does not have an adverse effect on cognitive function? Isn't that one of the problems? It may not be in a year, it may not be in two years.

DR. MURPHY: That is the question, how does one determine that if this may not occur during the immediate therapy that you can define the adverse event during the trial, or is that simply something we have to accept.

DR. WOLFF: What I wondered was whether cognitive development really means cognitive development or you have

some hints about other, more objective, you know, other than psychological tests.

DR. TEMPLE: The suggestion of following people who do well on either drug or placebo has some problem with it. The population that does well on placebo might be cognitively different from the ones who need a drug to get better, so that the loss to follow-up might what statisticians call informative, I think I am using it right, and you might be misled by that. It's not a randomized trial anymore. So, it's treacherous. You might choose to do that anyway, but it could be misinforming.

DR. CHESNEY: Dr. Wilfond.

DR. WILFOND: It certainly does strike me that one of the approaches that people have taken is following people for a long period of time as the natural history studies, epidemiologists do this all the time, and while they don't have the advantages of a long-term control trial with accurate data collection in a prospective study they can still get lots of information that will accumulate over years, so that does strike me as one approach that could be used more commonly than it currently is.

DR. TEMPLE: I think people are encouraged to try, but subtle differences in epidemiologic studies are treacherous. If there were a controlled way to do it, then, you would really know.

DR. FINK: If we look at the experience with asthma where there has been some data collection, there are two problems I see arising in even attempting to do this. One, in adults who were asthmatic as children, less than 30 percent recall a history of childhood asthma at age 30 even though they were hospitalized and on multiple medications.

Secondly, we have an epidemiologic study that shows that there is an increased risk of glaucoma and cataracts at age 65 with a five-year exposure to inhaled steroids within a lifetime, and yet everyone feels that the new inhaled steroids are safer.

Are we going to demand 65-year studies of new inhaled steroids to try and see whether they have a lesser risk of glaucoma?

So, I think it is laudable, but anything short of a national database that records all participation in clinical trials and treatment with prescription drugs and over-the-counter treatment is going to come up short of answering the question.

DR. CHESNEY: Dr. Gorman.

DR. GORMAN: I wanted to follow up on my colleague's down the table question. What did you mean by cognitive? I immediately narrowed that down to intellectual function, but is it also personality development? I mean not in terms of their major disease, but in other

personality development. Do people who are on Prozac not become captains of their football team?

DR. MURPHY: We were limiting it, maybe improperly, to learning, intellectual abilities, not to all other possible behavioral or personality adverse event potential, but to long-term learning and intellectual development.

DR. GORMAN: Meaning just the intellectual functions.

DR. MURPHY: Yes.

DR. TEMPLE: There are certainly other questions that might arise. You might wonder about sexual development, for example, to pick a possibility for that class of drugs.

DR. GORMAN: More concerned about sexual behavior perhaps than even sexual development.

DR. TEMPLE: Yes, that is probably what I meant.

DR. CHESNEY: Dr. Nelson.

DR. NELSON: I think from the discussion, most of us probably feel that it obviously is ethical to try and get this information. That is the way the question was phrased in the first place, but if you thought that at best you could get some sort of long-term registry kind of data, is there any leverage one has in asking for it particularly after a drug is approved?

Effectively, you are talking about a long-term, postmarketing registry of individuals on the drug to be able to get a hint of whether there is anything going on or not regardless of how hard that might be to conclude, but is there any way that you can ask for that and have it stick?

DR. MURPHY: Let me not go to that last question first. I think that the issues are on a registry, particularly people use the word national database, there would be issues of confidentiality that would be of concern.

I think also when we look at some of the very limited long-term trials in pediatrics that we are trying to take to undertake in other areas, the endpoint measurement, these other fields where you have a much more concrete endpoint is extremely difficult, and I think we are very concerned about what endpoint you would be measuring unless you--I mean somebody was telling the story about SATs or, you know, and we don't know what that would be.

So, I think we have at least two major issues just from a very pragmatic perspective, which would be the confidentiality issues and the lack of certainty of the endpoint measurement in this type of long-term trial.

DR. CHESNEY: Dr. Luban.

DR. LUBAN: The one thing that I wouldn't totally put out of the picture is limited registry data on selected cases, selected drugs, and selected patient populations. I

will give for an example the hemophilia population where certainly registering of those patients in serial follow-up, much of which has been paid for by the pharmaceutical industry, has provided a vast amount of information, very, very valuable, and very necessary not only for adverse events, but also for tasks of daily living, school attendance, and whatnot.

DR. CHESNEY: Dr. Danford.

DR. DANFORD: Not only does the length of follow-up present a problem here but also the breadth of diagnoses that you might be considering. So often, children diagnosed with depression don't have that as their sole diagnosis, but there are other behavioral and psychiatric diagnoses that can accompany depression, each of which may have an impact on intellectual development.

So, I would imagine not only a very long study, but a very large sample group to allow for those confounding influences.

DR. CHESNEY: Dr. Roberts and Dr. Murphy, would you like to move on to Question 1, and if so, could either of you maybe rephrase that or give us a few more specifics, or would you like to continue on Question 2?

DR. MURPHY: I think it would be helpful on Question 1 to just focus in on the actual example in which we have issued written requests. As we said, we have no

approved therapy in children. We feel that we do have a history of failed therapies, products approved in adults, but failed in children, and that we feel that it is important to be able to answer whether the therapy is effective in children.

We are asking for two trials, and this type of trial we feel is appropriate for this situation. Is there a situation in which you have a chronic disease that you would not feel that this is appropriate?

We heard some of that this morning, and I guess this would be your opportunity to say where you do not think this would be an appropriate trial.

DR. CHESNEY: Dr. Ward.

DR. WARD: Dianne, I guess I would think that children with bipolar disorder at significant risk for suicide would not be one that you would want to randomize to a placebo necessarily as opposed to all the difficulties that were described this morning about equivalence, that they probably warrant active treatment.

DR. MURPHY: So, you are saying the approved therapy in adults should be taken and basically extrapolated to children?

DR. WARD: Yes, because we actually have some therapeutic guidelines about monitoring, for example, if we would use lithium or if we used valproic acid for bipolar,

and those have defined therapeutic ranges.

As a neonatologist, I will confess to being well out of my level of clinical practice here, but I do think that those particular children would be at risk for deleterious effects on their health by not being actively treated.

DR. CHESNEY: Dr. Botkin.

DR. BOTKIN: I just had a question of clarification. What is meant by approved, does that mean FDA approved or does that mean approved by the community of physicians either here or perhaps in other areas like Europe or Asia that might have considerable experience with particular agents?

DR. MURPHY: In this scenario, we are speaking to approved meaning FDA approved for use in children meaning it has been studied in children.

DR. BOTKIN: Well, that certainly raises the possibility of whether you may need to have a third arm in those circumstances where the medical community is widely using an agent that, for whatever reason, is believed to be effective, that may need to be included as part of the clinical trial.

DR. CHESNEY: Dr. Geller.

DR. GELLER: Bipolar is my bailiwick. I think that everything everybody has said about looking at

depression and bipolar is true. It is very complicated. But the major problem has been that the drugs that are effective in adults don't seem to work in kids.

Some of it may be because the kids present more like severe adults, and they are very comorbid and there may be all kinds of diagnostic reasons. So, you really get into a problem is you want to do add-on studies of what you would consider a standard therapy.

I think this has been one of the reasons that has kept the research from going on is people don't want to give them placebo because they are suicidal and so sick, but if you don't, you can wind up doing things you don't mean to.

For example, there is rather good data now, valproate in teenage girls is elevating testerone levels and producing later cysts of the ovaries. The reason the data came about was looking at it in children who were female and epileptic, but it is already in very widespread use in bipolar girls who are teenagers.

So, I think that that has to be weighed against what you are losing if you have a placebo arm, and I think a very good argument can be made that you would want to hospitalize the children and study them where you can look at them, which has been a terrible problem in child psychiatry because all the inpatient units are closed.

I work at Barnes Hospital at Wash U. Barnes has

closed its inpatient child and adolescent psychiatry unit, something that would have been unthinkable, and it is impossible to have them on placebo on an outpatient basis in good conscience unless you are essentially hospitalizing them at home, which can be done, but at an expense now that with all parents at work now, there is not even one parent who is at home to do it.

We used to be able to do studies like that, and one parent would be at home, but now almost every family has two working parents. So, I think there is a succession of things that are needed, and one is there has to be some financing for inpatient research for children who have severe depressions and severe bipolar disorder.

Then, you can have placebo arms, and then you can find out what works in this age group, and that then can be a prelude to the longer term studies.

Just one final point. The question was can you look at cognition in children who are bipolar and depressed, and the answer is it is very difficult because most of them, even if they are otherwise brilliant during episodes, which tend to be very chronic in kids, they are failing in school, they are not functioning at all, so any improvement, whether it is related to drug or not, is going to make it look as if they are functioning cognitively better.

So, it is really going to be hard to decide what

you are going to use as baseline to compare long-term follow-up to. It may make more sense to use the baseline the first time you see them with 50 percent improvement or something as the baseline for later follow-up.

DR. CHESNEY: I think Dr. Spielberg was next and then Dr. Fost.

DR. SPIELBERG: I think Dr. Geller really summarized our quandary very effectively. There is one additional confounder, and that is total numbers of patients available even if we had the units available to hospitalize them and to do the studies.

The number of children is very small. As we have recognized in pediatrics in the past, the requirement for two, well-controlled studies has often acted as a disincentive. We have been told we really do have some real problems extrapolating efficacy from adults here, so we do have to come up with pediatric study designs, but remember the number of drugs out there, the number of classes of drugs out there, the number of new therapeutic classes coming down the pike, and then the number of children available to study even if we had the units available.

We are going to have to come up with some new paradigms, and I think we are probably going to have to come up with some new paradigms rather urgently of how to evaluate these drugs in the smallest numbers of children

possible, in the shortest duration of time, so that eventually, we can get to the point of doing comparative studies among different agents, and see which agents do and don't work. We are going to run out of patients very quickly.

DR. CHESNEY: Dr. Fost.

DR. FOST: I was going to say that the issue is not doing the placebo-controlled trial, but monitoring, that is, it would be okay to do it as long as children are radically monitored until Dr. Geller said it would be unconscionable to do this in an ambulatory setting, but then you also said that you thought the adult drugs were largely ineffective, so I am a little confused.

Why is it unconscionable if there aren't any effective treatments out there?

DR. GELLER: That is an excellent argument that as you can imagine, many people make to their IRBs all the time. The problem is that nowadays with families having both working parents, it is very hard to find somebody who can monitor a suicidal child on an outpatient basis.

If you had the child on no treatment, it would probably be impossible to get families to agree to be in the study.

DR. FOST: What treatment would you use?

DR. GELLER: What people are using clinically you

mean?

DR. FOST: Treatments of no known efficacy is what you are advocating?

DR. GELLER: I am not advocating that we use treatments that have no efficacy. What is being used clinically is people are just purely extrapolating from adults.

DR. FOST: But I thought you said that that seems not to be working.

DR. GELLER: If you look at the naturalistic data, our naturalistic data at the end of six months was that only 15 children out of a sample of 93 had recovered, and this is very, very different from adult data on bipolar where you get much, much higher rates of recovery. Only half the sample were receiving appropriate drugs, the disease is under-recognized.

Naturalistic, they were followed by their own practitioners, but even those who were followed by practitioners giving them adult drugs, in adequate doses for an adequate period of time, they still were not responding and recovering.

DR. FOST: Well, it sounds to me like you are describing a situation where there is no known effective treatment.

DR. GELLER: That is essentially the case for the

kids, which is why I think you need placebo arms if you are going to make comparisons, but I think if you are going to do that in a way that is going to be, as we are talking about, in an efficacious way, that you are going to need some inpatient units where suicidal kids who aren't on medication can be, so that parents and the community will accept it as a reasonable study.

I think we are essentially in agreement and talking about just some logistic concerns for this population.

DR. MURPHY: I am going to try to summarize that conversation. What I have, I think I heard here, is that for depression, where we have known studies with products that are approved in adults do not work in children, we need to do placebo-controlled trials because otherwise we will never know or we will continue to experiment on our children without ever having an answer; that we have real problems when we get into various other diagnostic entities in this area, and we have to find a way to study them in the placebo-controlled trials in a safe way, so that the children are not at any more risk or hopefully would be at much less risk than just trying a drug hoping--because they will be in the outpatient--hoping it works, and it may not.

Is that a fair summary?

DR. CHESNEY: Dr. Temple.

DR. TEMPLE: At least in the bipolar setting where people are using drugs like valproate and lithium, you probably could do an add-on study even though you don't know those work of some more conventional antidepressant against a placebo. That still leaves the problem of leaving them outside the hospital, a problem I have no solution to.

The other possibility is if those drugs really work so poorly, an effective agent might well be able to beat them, so another possibility is being better than the putative active control.

DR. FOST: Joan, the issue of leaving them outside the hospital seems to me analogous to the AZT trial argument, that is, no one is going to be worse off. Out of the hospital is where they are anyway, so nobody is going to be worse off. So, half the kids in the trial might be better off, the other half will be exactly where they were before. You are not introducing any element of harm by doing such a trial.

DR. CHESNEY: Dr. Geller.

DR. GELLER: I think intellectually I have full agreement with what you are saying 1000 percent. I think this is more an issue of the logistics and how you are going to do the studies with a relatively small population compared to the number of adult bipolars in a way that will give you answers in a reasonable amount of time, and this

requires having families who will agree to have their kids in the study. I think then you get into other kinds of issues of where the kids are safe, and so on.

DR. CHESNEY: Two more comments. Dr. Nelson has been patiently waiting and Dr. Gorman. Then, we probably need to go on to Example C.

DR. NELSON: I just want to keep the question about the purpose of the relapse prevention trial on the table, because I certainly haven't been convinced that there is a need for that, and it would bother me if you had a responder, given all this discussion of the lack of any evidence that anything works, and than randomize them back to placebo.

So, if I was reviewing that as an IRB, I would ask the investigator to give me a good scientific justification, put a lot of safety mechanisms in place, and nothing I have heard so far convinces me that that is necessary.

DR. CHESNEY: Dr. Gorman.

DR. GORMAN: I want to go back to Question 2, which was the cognitive development issue. Depression remains, at least in my clinical practice, a severe enough disease that I would want effective therapy to be available and approved even with that holding over my head for a long-term concern, just like for cancer chemotherapy, it's a disease that has severe morbidity and mortality, and even

though I know radiating their brains will decrease their long-term cognitive ability, I still would like to have that treatment modality available to me today for their survival.

DR. CHESNEY: Dr. van Zwieten.

DR. VAN ZWIETEN-BOOT: One of the questions was about two placebo-controlled trials, but I got the impression that during the trial, you put together children and adolescents, and that is something that we have been discussing in Europe, whether or not that is suitable certainly for depression.

First of all, the way the disease or disorder is expressed may be totally different. The course of the disease may be different. The endpoints, at least the scales that you use, may be different. Even if they have the same side effects, they may be felt different by adolescents and children. Sexual dysfunction is not something you will see in the younger children, but it certainly may affect adolescents that are just coming into puberty a lot more, and the other way around for other side effects.

Anxiety or what we see hyperactivity may be much more important for the younger children, and therefore, we tend to say that you should do separate trials, at least analyze them separately, but that means that you have to power them in such a way that you better can do separate

trials. Did you consider that?

DR. MURPHY: We always consider whether we should do the older age group first and then go down to the younger age group. I think the approach is that we would have the appropriate diagnostic tools and assessment tools that would be age appropriate.

Tom, do you have any other response to that?

DR. LAUGHREN: It is actually a little bit murky what the specific requirements are. Basically, where we have ended up is that we want at least one trial that essentially stratifies to both strata, but would probably accept replication in one or the other for the second trial as sort of a compromise, you know, given how difficult it is to do these studies and the fact that some of these trials were already started at the time that we were negotiating with the companies.

But given the history of completely negative outcomes in the older class of antidepressants, we did feel that it would be very hazardous to extrapolate from the adult data. So, that is the basis of our requiring replication in the younger population.

DR. MURPHY: So, I think that what we are saying is that if you did do a study in the older, you would still need to do the study in the younger.

DR. CHESNEY: I think we probably should move on.

We have only got 35 minutes to do Example C, which is the withdrawal phase. Dr. Hirschfield is going to present the two different types of patients for Example C and tell us which questions we are to address.

Example C: Pediatric Placebo-Controlled Clinical Trial Design Including a Withdrawal Phase When There is Only One or Limited Effective Therapy

DR. HIRSCHFIELD: Good afternoon.

We have been hearing all day since the early hours about the withdrawal study design, so we would like to present two examples and then move the discussion to focus on Question 1 and then 3 following.

The first example is an asthma study. The patients are considered stable, but they continue to have intermittent exacerbation on their current therapy whatever it may be, whatever combination of drugs might be required to maintain that level of control.

There would be standardization of care using a specified inhaled corticosteroid during the run-in phase of the trial, and we would say the length of the run-in phase would be adequate to establish whatever parameters might be needed.

That would be followed then by randomization to either an active control, the study drug or placebo during the withdrawal phase. So, there are three arms, and each

one would get at least their standard of care plus then the active control, the study drug, or placebo.

There are specifics which for the sake of brevity I may skip over in reading through the sheet on this trial design, but we could answer any questions for clarification that might be needed.

We will move to the second example, which would be the hypertension example.

This condition is considered chronic, which would require long-term therapy. The patients have mild to moderate hypertension. The mild to moderate is defined by the age-adjusted criteria for blood pressure.

We are looking in this particular study design at children who are in early to mid puberty, so we will say 12 to 16 years old, males and females. They have their mild to moderate hypertension controlled by medication relatively stable, so now they have a run-in period which we thought would be a fairly lengthy run-in period of anywhere from 3 to 6 months, so that they are stabilized through the range of their activities.

They receive this study drug for that period of time. They have their blood pressure measured at the same time daily. Then, they are randomized, and they will be randomized to receive the study drug at the same dose or the study drug at a somewhat reduced dose or at a very reduced

dose, zero, so they are getting placebo at that time.

They will continue to have their blood pressure monitored, and in this trial and in the asthma example, on an individual patient basis. There are prospectively defined, explicit criteria for escape, for rescue therapy, or whatever else would be discussed in the protocol, and the patient would then be discontinued from the study when these criteria were met.

Of course, it goes without saying, but I will say it anyway, that safety is included as part of the assessments.

So, now we come to the question specifically. In these two examples, we are asking about the applicability of a withdrawal study design to learn about both efficacy and toxicity over a relatively extended time period.

Both examples have a lead-in time when all patients receive the same therapy after which they are randomized, so that some patients continue to receive active therapy while others receive placebo.

An important element of these examples is the presence of well-defined conditions or rules for discontinuation of the patient from the study and treatment with active therapy.

Our first question is: Do these examples represent an acceptable level of risk for pediatric patients

in a clinical trial?

DR. CHESNEY: Thank you.

Dr. Nelson.

DR. NELSON: I feel a little differently about either one of these trials. I know that we have turned down as an IRB a trial that involved a placebo group for children that we thought were on steroids and would have been then taken off steroids in asthma.

I think the reason why I might feel differently is certainly seeing the short-term risks of both morbidity and mortality related to asthma, and the variability in standard of care and access to care that occurs within certain populations, that the risks of asthma--and this may just show my bias working in an intensive care unit--strike me as much different than the risk of hypertension, which might be off medication for a certain period of time where there may not be any short-term risk as opposed to long-term risk. That bias may just reflect my clinical practice, so I am happy to be corrected on that second point. I think that is why I feel very differently about these two trials and the placebo group in particular.

I wouldn't be very happy with the placebo group in the asthma. They are certainly not on standard of care. It is a very different example than the other one, and I don't think you can put safety mechanisms in place to prevent that

frankly.

DR. CHESNEY: Dr. Fink.

DR. FINK: I guess I would take the other approach to the asthma trial. It would concern me, but I think it would be ethical and doable as long as the parameters for failing were set adequately, and that is, if you monitored pulmonary function or peak flow so that you had early indication of failure and did not wait for emergency room or hospital admission as your endpoint of failure.

Peak flow, if done properly, is probably every bit as accurate as blood pressure in hypertension, and peak flow would give you an early indication of failed therapy, so you could set it high enough to prevent exacerbations that were clinically significant, but it might, with the natural variation in asthma, lead to a lot of treatment failures in that placebo group, which would be just fine.

DR. NELSON: I think rationally, you could design it that way. The real world would be that it would be that it would be potentially done in situations where children didn't have that easy access.

What worries me the most about a lot of these studies in terms of my own bias is having non-pediatric IRBs approving them, and then these kinds of studies being done in situations where the basic framework of health care is not well established where children are getting care because

they lack adequate access, and where frankly, I don't think the people doing them are going to have the systems in place just for general care that can do it safely.

Certainly, you can design it, and some groups could carry it out safely, I agree.

DR. FOST: Skip, would you be comfortable--it sounds to me again like a monitoring problem, not a design problem. That is, if it were restricted to populations or individuals in which there were assurances that monitoring was adequate.

DR. NELSON: I would admit it's an open question. I would be very nervous about it, but it would be open for discussion, but the difficulty is that studies like these, once approved, are not restricted to those circumstances.

DR. FOST: But that could be a condition. The IRB would require it, and you could monitor it through periodic review.

DR. FINK: Since we are getting to asthma trials, this raises an issue I would like to I guess bring back to the FDA. To date, FDA has required manufacturers to provide products or label them only for sale in the same format they are used within a controlled clinical trial, and at least for all of these discussions of inhaled medications, one of the primary problems is what is the adherence or compliance with taking the drug, and there are devices, computerized

devices that can be used with the standard canisters, that have not been used in these clinical trials because the manufacturers don't want to be burdened with having then to provide those for clinical use.

Has the FDA considered allowing a controlled clinical trial to use compliance monitors that would not be part of the package labeling or be required for sale?

DR. TEMPLE: There are trials that are conducted with certain kinds of compliance monitors, SMART bottles, and things like that, that are definitely not part of the approved labeling. They are just designed to optimize the available study.

Were the things that you were describing ways that alter the delivery, though?

DR. FINK: Well, that argument comes up that, for the metered dose inhalers, if you use one of the devices that has a potentially different pore size, it could alter drug delivery although it is probably a small effect compared to the adherence or compliance monitoring you get from it, and some of the manufacturers are trying to develop compliance devices that get around that issue.

DR. TEMPLE: Those are worrisome. As you obviously know, the use of spacers with a lot of metered dose inhalers is widespread and by no means all of those have actually been tested with any particular product. I

would say we find that troublesome, but don't quite know what to do about it.

Where a spacer or something like is recommended for use with a particular product, we do ask that it be studied with that product. It's a thorny problem. Pore size and things like that affect delivery and every aspect of the effectiveness of the treatment, or at least that is what our pulmonary people certainly believe.

It would be difficult for us to label it for use in a completely different way from the way it was studied. Maybe that is something that bears more discussion.

DR. MURPHY: We are trying to ask in our written request that the products are studied in the way that they are going to be used. We are looking at that and trying to make sure that those various devices that will be used by children are looked at.

DR. FINK: It seems like there is an over-emphasis on the devices, though because if you were going to logically take that stance, then, a metered dose inhaler that was shown to be effective in a controlled clinical trial should have in its package labeling that this medication has been shown to be effective when there is every two-week follow-up medical care and review of proper inhaler technique, because I would maintain that although there are some delivery differences based on pore size,

compliance and use of the device and how often you re-educate the patient are much bigger issues, and yet your package labeling doesn't say that they have to be seen every two weeks like they were in the controlled clinical trial even though you are harder on the devices.

DR. MURPHY: But the point of many of our labels are to describe the situation under which the trial was conducted, so that you understand that those are the circumstances in which this was proven to be efficacious and safe, knowing that every step beyond that, that you take, you impact it, because we can't possibly study every variation that may exist out there, and certainly we don't want to impact or try to modify the physician's ability to do what the think is best.

So, that is why the label had in it how the trials were conducted.

DR. TEMPLE: But you are actually making a point that has been made by a lot of people in a slightly wording, that perhaps we should be studying what they call the effectiveness of drugs, that is, outside of the confines of a very rigid trial, and we have not regularly asked for that.

One of the reasons it is difficult is that as soon as you introduce a control, especially a placebo control, nobody believes it is a naturalistic setting anymore, so it

is not easy to study true effectiveness except epidemiologically and for the effect sizes that are seen here, epidemiologic studies and studies in HMOs are not very good. Now, maybe for something hugely effective like a steroid, maybe that would work, I don't know.

We have generally not asked for trials of that kind, but I would say there is growing interest in seeing whether less monitoring and things like that leads to a major compromise in effectiveness.

But it is certainly true, what is in the labeling is trials done the way trials are done, very frequent monitoring. I mean the hypertension trial, people will be monitored every two weeks. No one thinks that is what you should do in practice.

DR. CHESNEY: Dr. Kauffman.

DR. KAUFFMAN: I wanted to come back for a moment to the hypertensive illustration, because that has been a major problem for us in the PPRU.

With respect to 12- to 16-year-olds with mild to moderate hypertension--and I assume although it is not stated this would be individuals who have no apparent end organ involvement at this stage of their life, they are essentially healthy kids--I think I could live with this study protocol very easily and agree that this is an acceptable level of risk, particularly since most of these

people are capable of participating in the consent process. They are old enough to understand a lot of the risks.

The real problems here are not the theoretical ethical considerations, the way you have laid it out, it's the practical considerations and it has to do with how do we standardize blood pressure monitoring, and that is a major problem we have struggled with.

Blood pressure in this population is very labile, and it is hard to establish that they have mild to moderate hypertension over a prolonged period of time, particularly months, consistently. We are supposed to treat them with, quote "diet," and nonmedical means in this diagnostic category. It never works because they don't do it, but that is what we are supposed to do.

It is hard to keep these kids coming back for this frequent a follow-up. There are just a lot of very practical issues that get in the way of doing what sounds very good theoretically, but really ends up bringing ethical considerations to bear because of our inability to consistently do the ideal.

DR. CHESNEY: Thank you.

Dr. Gorman.

DR. GORMAN: I guess to follow up on Dr. Kauffman's comment, the placebo arm in this group would have to have diet and exercise, and even though it is

problematic, as he brings up, it is also shown to be effective when it is performed.

So, a true placebo, by "placebo" in this particular case, I hope he means pharmacological placebo, not care.

DR. CHESNEY: Dr. O'Fallon.

DR. O'FALLON: This particular design struck me as the best from a point of view of evaluating the effect of a given agent of the three that we have looked at today. This one seemed to give you the best information about the actual performance of a therapy.

But what troubles me about this one and the last one, which is what I was going to say, is the endpoint measurement seems to be such an issue. I thought, because I have not a physician, I thought that you would know when they failed, that that was a fairly clear thing, a doctor taking care of that patient would know when they wanted to stop that therapy.

That would be absolutely essential somehow or this wouldn't work.

DR. MURPHY: I think what you were hearing is that there are different levels of failure, and what is important is where you set that level of failure, and when we heard that failure where you end up in the intensive care unit is not acceptable.

Failure where you have a change in your peak flow might be, and that we would need--also, what I heard is we would need some sort of other external monitoring to make sure that we didn't have so many of these in one arm that it was unethical to continue the study.

DR. O'FALLON: Those measurements, though, we were hearing about how highly variable the blood pressure measurements were. Definition of failure at the endpoint. He was worried about going in on the front end, I was more worried about coming out on the back end, when would the doctor pull the plug on the therapy, because they were convinced that the patient had failed.

DR. MURPHY: Actually, one of the questions we eliminated was this sort of getting at some of these issues, which is a very long lead-in, so that you would get hopefully beyond some of the issues of is it real or not, that it is sustained, but not to the point where you felt that you could not intervene, that you would have the alternative approach of the intervention being diet and exercise, all the things we love to talk about and know are so hard to do.

DR. KAUFFMAN: There are technical ways to do this now. For example, continuous monitoring at home, and so forth, that are getting us to where we need to be here, so I think we can get around some of these.

It is hard to enroll in these because people don't want to do all this stuff. They know what works.

DR. CHESNEY: Dr. Crawley has had his hand up, and then Dr. Temple, and then I think we should probably go to Question 3.

Dr. Crawley.

DR. CRAWLEY: I just had a more general question in a certain sense. When I look at the question that is presented to us here, do these examples represent acceptable level of risks for the patient, I think we all here in the room have the children in mind as being in our best interest, but what I am hearing in the discussion of the case studies today is largely with regard to the design of these trials, so that they are in the best interest of the patients.

But what I am missing myself, and I was just wondering how the committee planned to address that, is really the voice of those patients, the presence of the patients, of the children, and I know it is not a simple question or an easy task, but I was wondering how they could be integrated into the discussion.

What I see largely around the table are top-level professors in Pediatrics who have the best interest of the patients in mind, but in the discussion on what is acceptable for the patient and what is of the interest for

the patient, I think it is not only the design of the study itself that is of interest, but also that communication and that dialogue with the patient that is of importance.

Thank you.

DR. CHESNEY: Could I just ask Dr. Kauffman to comment on that because it is my impression that these PPRUs are to some degree addressing that issue, is that correct?

DR. KAUFFMAN: I am not sure what you mean. At our place, we did a retrospective survey several years ago, our coordinators did, to try to glean from 60, 70 kids who had participated in clinical trials what their perception of it was, and these were kids 5 to 16 years of age, and overall, they reported back that it was a positive experience, they would do it again if they were given the opportunity. Over 95 percent of them said that.

I think Dr. Nelson has much better perspective data that we do on this. He may not want to talk about it at this point, but I think he is doing one of the things that needs to be done to try to get at this issue, how do kids feel about this experience and what is their perception of taking risks or getting benefits from being in a study.

DR. NELSON: What Ralph is referring to are some focus groups that I have been doing, which is hard to summarize. I think every child is going to be different, and I think part of the challenge is being able to construct

a trial to allow them to demonstrate that difference ranging from kids that wouldn't want to come close to this kind of a study to others that I recall. I did a focus group at Ralph's place, and one 9-year-old, who gave an analysis of placebo-controlled study and talked about the two arms and said I would be happy to participate. I mean I am sitting there, jaw hit the table.

So, there is a lot of variability, and I am trying somehow to design things in a way that would allow them to do that, but the other caveat is, you know, that voice I think needs to be set within the context the parental obligation to protect, as well.

The relationship between the parent and the child, and the parent being able to feel that that voice is within the framework of the ability of the parent to protect the child from risks that they wouldn't otherwise want that child to be under.

It is kind of where I have my doubts about the asthma, and I am less doubtful about the blood pressure. I think knowing the reality of how most asthma care is delivered in many parts of the country, which is poorly, that is partly what bothers me, just about the framework within which this kind of study would impact in terms of the parents' access to health care.

DR. CHESNEY: Dr. Santana and then Dr. Temple, and

then we need to go on.

DR. SANTANA: I guess what I heard our colleague from across the ocean say is something completely different. What I think he was challenging us to think is that these studies may be okay to do, but we need to think of parallel studies that go with these to give us a really better understanding of what kids know that they are getting into and that they have a true comprehension of what these trials are asking them to do.

In a study that somebody at St. Jude did, looking at Phase I trials, and end-of-life situations in kids with cancer and whether the kids truly understood what a Phase I trial was and if they had their choice, what was their choice, and you would be very surprised about the type of responses that this person who was doing the research got.

It's that most of the kids did understand what a Phase I trial was, and they made the right decision when they wanted to participate.

So, I think the challenge is that we don't have to resolve the issue here today, but that some of these very controversial studies should have parallel studies that help us get a better understanding of what the kids are truly understanding, and they really know what they are getting into.

DR. CHESNEY: Dr. Nelson wanted to make a final

comment.

DR. NELSON: Yes, I begged for one last comment. One of my concerns in this arena with the threshold about placebos is particularly if you are looking at certain endpoints that rely on symptom reporting, which within a trial is the extent to which children report differently, and I don't think we have really any information about how endpoints that rely, not on sign recognition, but on symptom reporting, how that would be impacted differently in a pediatric as opposed to an adult trial.

So, that is one question that causes me to worry about the death or irreversible morbidity sort of threshold in placebo criteria.

DR. CHESNEY: Dr. Temple.

DR. TEMPLE: I don't have anything about the rather interesting discussion that just took place. I just wanted to observe that if managing to follow kids because of the complexity of their lives is difficult, these kinds of designs to some extent minimize the period of intense follow. You can monitor relatively infrequently during the lead-in period and much more intensively even for a matter of days, for example, in a hypertension trial to see whether they have escaped.

DR. CHESNEY: I think our last question before the break is No. 3. What role, if any, does a DSMB play, is it

necessary for the ethical conduct for each of these trials to have a data safety monitoring board?

Dr. Fink.

DR. FINK: I would like to raise an issue here, and I don't know what the number is, but I think one issue that should be looked at carefully is that a data safety monitoring board may be much more important in the typical multicenter trial where each individual center may only enroll 8 to 10 patients, because in that kind of setting--and it is very common in the asthma trials--no individual center has a good feel for the side effects, adverse reactions, or problems that are occurring in the overall trial, and as the trials get spread over more and more centers, as is commonly done, the ability of someone to have oversight of the entire trial is really lost.

I don't know if the magic number is 10 or 20, but at some certain number of centers involved in a trial, an oversight board I think becomes probably more advisable.

DR. MURPHY: In pediatrics, this problem is magnified, the fact that we have small numbers frequently and need large numbers of centers.

DR. CHESNEY: I think that emphasizes the point Dr. Kauffman made also, they are probably most important in the larger multicenter.

Other comments? Yes.

DR. FINK: The one other concern I have with this discussion of what is ethical, we are evolving into fairly sophisticated study designs, and at least in some diseases, like asthma, I think we have already seen that it has the effect that it tends to exclude minority populations from participation in controlled clinical trials, and I don't know if that is something the data safety monitoring board should be taking on, but somehow we need to ensure that minority populations are adequately represented, because the typical asthma trial that is performed today is 80 percent suburban white participants even though the vast majority of asthma and the burden of it falls on inner city blacks and hispanics.

DR. CHESNEY: Why is that?

DR. MURPHY: I think we actually did address the issue of adequate enrollment of minority populations in the asthma trial. Maybe we didn't put it in here.

DR. CHESNEY: This is ignorance on my part. Why are the minority populations not being included? Is it for compliance or unwillingness to participate?

DR. FINK: Some of it I think is difficulty in getting informed consent. As a clinical researcher, the other thing you look at is your study coordinators want patients where it is easy to collect the data and they will keep their visits on time, and they make data collection, so

that you tend to choose your best study subjects as the first ones you enroll.

DR. CHESNEY: Any other comments about data safety, monitoring boards in the setting of the withdrawal phase?

Dr. O'Fallon.

DR. O'FALLON: The comments that have just been made now about what a DMC could do, I see all that responsibility as being the part of the statistical center and the study team. I don't know how you define a study team for this sort of an asthma trial. I do know a fair amount about it in cancer.

You know the study team is a group of people who are actually running that study, and they are the ones that are responsible for the information that is coming out of the unfolding data.

A DSMB in a certain sense overlooks the conduct of the whole trial. I think you should have a study team in place that would be looking--and a data center--that would be looking at the adverse events and that sort of thing.

DR. CHESNEY: Dr. Gorman.

DR. GORMAN: I am still struggling for words in my non-ethical capacity to explain why withdrawal studies are so difficult for us, and when we randomize going forward, there is an equal chance you will get benefit or detriment.

Of course, you don't know. But in withdrawal studies, you are taking people who are on adequate therapy, no matter what it is, and you are taking them off of it, and I think that is a different ethical condition to be in.

I think that is why the IRBs that we have all sat on have had some difficulty withdrawing people from studies because in this case, you have people on appropriate therapy, and you take them off, and that is what makes these kinds of studies a little bit more difficult than randomizing people prospectively because you are taking people off of appropriate therapy, or therapy where they are well maintained.

DR. CHESNEY: Dr. Fink.

DR. FINK: I think Dr. O'Fallon brought up an interesting point. Some of that probably depends on the funding source. The majority of asthma clinical trials are industry sponsored, and as a result, there is no study group except for the company itself, and to the extent at which you trust them, and I don't entirely trust them.

I mean I have been asked to participate in industry-sponsored trials where it is clear the company was spreading the trial over multiple centers, so that every center was underpowered to detect a difference of effect, so that only the company would know whether their drug was effective or not, but no one participating in the trial

would ever have access to that data, and it is a very nice way for a pharmaceutical company to do a direct comparative trial at no risk because no single center has enough patients in the trial to look at efficacy.

DR. FOST: Let me help Dr. Gorman with his discomfort about withdrawal. The reason you feel uncomfortable is because you think you now have the patient on something that is effective, and if you know that, it would be wrong. The reason you are doing the withdrawal is to find out, and until you do the withdrawal, you don't know whether you have helped the patient or not.

DR. GORMAN: Agreeing with that intellectually. Clinically, it becomes much more difficult because you have put them on something somewhat randomly, you have randomized them at the beginning, and then you have an effect.

DR. FOST: You don't know that yet.

DR. WILFOND: Now, I think I can help you out because my point was also about that issue. What strikes me is that there are different populations that might be willing to participate in any of these trials, and I think those are people who, for whatever reason, are unhappy with their current care, who are desperate for better treatment.

I think those are the people who are at the greatest risk of being in a trial, whether it's an add-on or withdrawal study, because their expectations are much

greater in terms of therapeutic benefit.

On the other hand, people who are doing well often will raise questions amongst themselves or their parents about when is it time to stop this therapy, and it seems that people in that situation are ideal candidates for trials where treatment is withdrawn, because in that case the options are either withdraw outside of a trial and be monitored by your physician or enroll in a trial where there is a 50 percent chance of withdrawing, or perhaps being a drug that may be helpful, or you will find out.

I think that one of the things that hasn't been done is there hasn't been a greater emphasis on trying to encourage patients who are doing well to be in studies.

DR. CHESNEY: Dr. Danford and then Dr. Temple, and then we will let Dr. Temple and Dr. Murphy decide whether we have answered all their concerns.

DR. DANFORD: One last word of reassurance for Dr. Gorman would be the reminder that drugs do have risks and adverse effects, that you would be taking away the potential for those risks and adverse effects in half of your patients as you withdraw.

DR. TEMPLE: The trials have somewhat different purposes. If patients are put onto a lead-in with a drug, and appear to respond, you really don't know whether they responded to the drug or not. If they are part of a

randomized trial, then, you might know.

So, you really are--I guess Dr. Fost said--you are just finding out whether it is really working for them at the end of it.

The other use of these trials is to take a drug that you are quite sure works in the short term, and examine whether it continues to work for the long term. That, I guess, is a little different because then you are fairly sure you are giving the person something that is effective, but as someone said, you want to find out whether it continues to work, you want to see what the consequences of withdrawing it are, because drugs do get withdrawn, so there are things of interest to the patients even in that setting.

In the first case, you really don't know that it worked, it just sort of looked like it did, you don't really know.

DR. CHESNEY: Dr. Murphy.

DR. MURPHY: I think what I heard from this last bit of discussion was that in the withdrawal trials, if we can define the population that would be involved in a withdrawal trial, so that the population is either at minimal risk because you are going to be able to define early enough what the failure rate is or early in the disease, and those are actually two different things, may involve two different processes.

Dr. Gorman, to get at your issue, certainly, in asthma where you have a life-long disease where you would like to have people come off of certain therapies after a while, if there is a way to define that population in the trial, that that might make it a more acceptable trial approach. Is that--no?

DR. GORMAN: I don't have any ethical difficulty with the study design. I think why it makes it more difficult, I know it is the myth that you are doing something good for your patient because you did something and they got better, but they are the ones who are now doing well, and you are asking them to withdraw.

Now, for asthma and for several other disease states where they are intermittent with exacerbations and calming down periods, I think a withdrawal study not only makes sense intellectually, but is required to prove the efficacy of these agents.

But the difficulty, the intrinsic difficulty is I am doing something good, and you are making me stop it makes it hard for institutional review boards, as well as individual clinicians, to enroll people in these kinds of studies, because the people are doing well, you want to continue to have them do well.

DR. MURPHY: We tried not to bring you anything too easy to answer today. I think that was quite clear in a

number of the questions.

DR. CHESNEY: I think Dr. Fost had one more comment and then we will probably take our break.

Dr. Fost.

DR. FOST: Just two brief ones. That psychological problem is the same as doing a prospective trial when there is a standard therapy out there that has never been shown to be effective. That is, you have people who are getting treated for something, and you think it must be good because everybody is doing it, and yet you don't really know.

But, Dianne, I would just hope one of the take-home points of both these examples, the add-ons with the placebo group, and the take-aways with people who you think are having an effect, is that adequate monitoring is what makes these trials ethically acceptable, and absent that, they wouldn't be, either one of them, if there is some possibility of serious harm coming to somebody.

So, the IRB needs to assure that selection of patients will be under circumstances in which they can be monitored properly.

DR. MURPHY: I think you saw that in our questions that that is one of the areas that we wanted to help bring forth in the discussion. We think that if we are going to be able to do what is necessary, which is to find out if

these products do work in children, and are safe, that we need to have a way.

Clearly, today, you have told us, and some things we don't have a way yet to do it, which are some of the long-term studies, but that we will have to go with the information that we are able to develop at the present time, and maybe in the future we will be able to come back to you with additional knowledge that we would be able to move in a new design because of additional knowledge, but for right now, for long-term studies, we will have to basically deal with what we know in our controlled short-term studies, and that we will also address the issues of levels of risk in both of these, both for the patient monitoring and the trial monitoring.

Yet, to address Susan's concern, I think it is clearly not possible to have every pediatric trial involved with the DSMB, nor probably necessary.

DR. CHESNEY: Dianne, could I just make one comment? I am really troubled by Dr. Fink's example and I wonder if you wouldn't develop some kind of recommendations for the pharmaceutical firms, that if it was a situation where there were multiple centers, and no one center was going to recruit many children, that a DSMB is strongly recommended or required.

DR. MURPHY: I think we heard that message that

multicenter trials, let's take away motivation, multicenter trials that are trials that we ought to look at considering DSMBs, particularly in pediatrics where, as we have talked today, we frequently have the problem of small populations.

As far as nobody is going it come to us and say, gee, we think we need a multicenter trial because that way we can sort of keep any lack of efficacy quiet. Usually, the reasons that are given are that it is difficult, and I mean we know this from adult trials, too, I mean this isn't a pediatric problem, that it is often difficult to get the numbers that you need in one place, and that is why we have multicenter trials, and that is the usual reason that we are given.

DR. CHESNEY: Dr. O'Fallon, last before the break.

DR. O'FALLON: We haven't even done anything with the value of multistage designs or spending functions and all that. We mentioned them and then dropped it, but I think such study designs are necessary no matter which of the designs you are going with, because they do have the ability to minimize the number of patients that are spent in getting an answer. They have the ability, they don't always work, but they have the potential.

DR. MURPHY: I think for those of us around in a couple of years, it would be very helpful to bring forward some of these trial designs that have failed in pediatrics

and some that have succeeded, so that we can look if some of the issues that you are bringing up have played into-- rather, they were appropriately monitored and stopped or not stopped when they should have been.

DR. CHESNEY: Let me thank all the speakers from this morning and particularly our international visitors, and we can take a 10-minute break now. We need to be back here at 3 o'clock, maybe an 8-minute break, for a discussion of psychotropic drug use.

[Break.]

AFTERNOON SESSION

Pediatric Psychotropic Drug Use Issues

Part 2: A Proposed Approach to the Development of Psychotropic Drug Therapies for Pediatrics

DR. CHESNEY: This afternoon's session is a discussion of pediatric psychotropic drug use issues. As I think you will hear from Dr. Murphy, there are a number of meetings scheduled over the next month or two to discuss this issue, and I think we are going to learn a great deal about what will be discussed at the upcoming meetings, and I think Dr. Murphy is going to lead off.

Introduction

DR. MURPHY: We knew you would just be invigorated at this time of day. We hope to do two things this afternoon. One, is to give you an update on what has been going on in this field, which is the drug development for psychotropic therapies, and secondly, is to have you comment to us. We realize this is a very short time, and we could use at least a day or two on this topic, but I will tell you what other avenues may be available to do that.

But we are moving forward now, and as we move forward, we want to tell you about our plans, and we wanted you to give us some comments as to a really sort of global perspective as have we forgotten anything that we should be thinking about or are we pretty much on target here, and

that is very crude way of stating the questions which you will hear in more elegant form in a minute.

If you weren't aware, this is an area of interest to the White House, and precipitated by some articles about the use of psychotropic therapies in preschool children, and there has been an initiative to bring this area forward for development as far as trying to define are children being undertreated, overtreated, appropriately treated, inappropriately treated with psychotropic therapies.

There will be next week a meeting sponsored by the Surgeon General and FDA to address a broader issue, which is the access to proper diagnosis, proper therapy, and, in addition, FDA will be there to talk about the concerns that we have, Tom Laughren will be presenting, in therapeutic interventions when you don't know how to make the diagnosis, and you don't know how to measure the endpoint. So, that is Tom's goal at the Surgeon General's meeting.

Because of the aspects I just mentioned, there is a difficulty in making sure that we have the proper diagnosis or that we have the proper way of measuring a response to a therapy, there will be a research meeting which NIMH and FDA are sponsoring in early October, and we have plans to look at a number of these very questions, such as are the diseases the same, are they not, what are we missing in the way of fundamental knowledge in some of these

areas or fundamental tools for diagnosing and measuring response to therapy.

At this point, I will turn the meeting over to the people who know a lot more about this topic. Thank you very much.

DR. CHESNEY: Jayne Peterson, our Executive Secretary, who you might also notice is a lawyer, tells me that we have to go through introducing ourselves again and following which she will read the Conflict of Interest Statement.

So, if we could start, Dr. Rodriguez.

DR. RODRIGUEZ: Bill Rodriguez. I am with the Food and Drug Administration. I have the title of Pediatric Science Consultant Director. Thank you.

DR. MURPHY: Dr. Dianne Murphy, Associate Director for Pediatrics at the Center for Drugs.

DR. LAUGHREN: Tom Laughren, team leader for Psychopharmacology at FDA.

DR. KATZ: Russ Katz, Director, Division of Neuropharm, FDA.

DR. GELLER: Barbara Geller, Professor of Psychiatry, Washington University in St. Louis.

DR. LUBAN: Naomi Luban, pediatric hematologist/oncologist, Children's Hospital and GW University.

DR. SANTANA: Victor Santana, pediatric oncologist, St. Jude's Children Research Hospital, Memphis, Tennessee.

DR. FOST: Norm Fost, pediatrician, Director of the Medical Ethics Program and chair the IRB at the University of Wisconsin at Madison.

DR. RODVOLD: Keith Rodvold, Professor of Pharmacy Practice, Colleges of Pharmacy and Medicine, University of Illinois at Chicago.

DR. HUDAK: Mark Hudak, neonatologist, Professor of Pediatrics, University of Florida at Jacksonville.

DR. NELSON: Skip Nelson. I am a pediatric critical care physician and chair of the IRB at the Children's Hospital of Philadelphia.

DR. CHESNEY: Joan Chesney, Pediatric Infectious Disease, in the Department of Pediatrics at the University of Tennessee in Memphis and Academic Programs at St. Jude.

MS. PETERSON: Jayne Peterson, Executive Secretary of the Pediatric Subcommittee with FDA.

DR. FINK: Bob Fink, pediatric pulmonologist at Children's Hospital, Washington, D.C.

DR. FUCHS: Susan Fuchs, pediatric emergency medicine physician, Children's Memorial Hospital, Chicago, Illinois.

DR. GORMAN: Richard Gorman, general pediatrician

in private practice in suburban Maryland.

DR. DANFORD: David Danford, Professor of Pediatrics in the Department of Cardiology Joint Division, University of Nebraska Medical Center.

DR. O'FALLON: Judith O'Fallon, Professor of Biostatistics, Mayo Clinic, and also group statistician for the North Central Cancer Treatment Group.

DR. RYAN: Neal Ryan, child psychiatrist, Professor of Psychiatry at the University of Pittsburgh.

DR. MALONE: Richard Malone, Associate Professor of Psychiatry at MCP-Hahneman University.

DR. WARD: Bob Ward, neonatologist, Professor of Pediatrics, University of Utah, and chair the American Academy of Pediatric's Committee on Drugs.

DR. SPIELBERG: Steven Spielberg, head of Pediatric Drug Development, Johnson & Johnson, representing PhRMA.

DR. CHESNEY: Thank you.

Now, Jayne will read the Conflict of Interest Statement.

Conflict of Interest Statement

MS. PETERSON: The following announcement addresses the issue of conflict of interest with regard to this meeting and is made a part of the record to preclude even the appearance of such at this meeting. Based on the

submitted agenda for the meeting and all financial interests reported by the committee participants, it has been determined that since the issues to be discussed by the Subcommittee will not have a unique impact on any particular firm or product but, rather, have widespread implications to all similar products, in accordance with 18 USC 208B, general matters waivers have been granted to each special government employee participating in today's meeting.

A copy of this waiver statement may be obtained by submitting a written request to the Agency's Freedom of Information Office, Room 12A30, of the Parklawn Building.

With respect to FDA's invited guests and guest speakers, Dr. Ralph Kauffman, Dr. Mark Riddle, Dr. Neal Ryan, Dr. Steven Spielberg, and Dr. Robert Ward have reported interests which we believe should be made public to allow the participants to objectively evaluate their comments.

Dr. Kauffman would like to disclose that he has grants with Bristol-Myers Squibb and is involved in research for Bristol-Myers Squibb, Astra, Zeneca, Janssen, Merck, R.W. Johnson, and Aventis, and is a scientific adviser for the Bristol-Myers Squibb, Johnson & Johnson, and Purdue Pharma.

Dr. Riddle would like to disclose that he is a researcher through contracts with Lilly Research

Laboratories, Smith Kline Beecham, Quintiles Pacific, and Pfizer, receives consulting fees from Excerpta Medica and Janssen, and is a scientific adviser to Shire Pharmaceutical.

Dr. Ryan would like to disclose that he has contracts with Smith Kline Beecham and Wyeth-Ayerst, and is a scientific adviser to Wyeth-Ayerst, Smith Kline Beecham, Pfizer, and Eli Lilly.

Dr. Spielberg would like to disclose that he is an employee of Johnson & Johnson. Dr. Ward would like to disclose that he owns stock in Ascent Pediatrics and Viropharma. He has grants with Wyeth-Ayerst, Novartis, Ascent Pediatrics, Aventis Pharmaceuticals, and Sepracor, and he receives consulting fees from Janssen Pharmaceutical and is a scientific adviser for McNeil Consumer Products.

In the event that the discussions involve any other products or firms not already on the agenda, for which an FDA participant has a financial interest, the participants are aware of the need to exclude themselves from such involvement and their exclusion will be noted for the record.

With respect to all other participants, we ask, in the interest of fairness, that they address any current or previous financial involvement with any firm whose products they may wish to comment upon.

Thank you.

DR. CHESNEY: Thank you, Jayne.

Open Public Hearing

DR. CHESNEY: We don't have anybody formally signed up to participate in the open public hearing, but this is an opportunity if there is anybody who would like to come to the microphone to make any comments.

[No response.]

DR. CHESNEY: I think we will proceed then. Our first speaker is Dr. Tom Laughren from the FDA, who is the team leader for Psychiatric Drug Products in the Division of Neuropharmacological Drug Products. He is going to speak to us about current regulatory issues in pediatric psychopharmacology.

Current Regulatory Issues in Pediatric Psychopharmacology

DR. LAUGHREN: Thank you.

[Slide.]

As Dianne mentioned, the goal of this afternoon's session is twofold. We are going to try and update you on certain events that have been happening in the area of pediatric psychopharmacology. I am going to talk about this area from a regulatory perspective, and we will have other speakers to talk about it from the standpoint of research clinical, and then Dr. Vitiello from NIMH is going to talk about it from their perspective.

Secondly, we would like to get some feedback from the committee on certain questions that, if we can address them, would help us to move this process forward.

[Slide.]

These are the topics that I want to talk about this afternoon. First, what I am going to do is very briefly review what approved indications there are in this area of pediatric psychopharmacology. It is a fairly short list.

Secondly, I am going to very briefly give you some background on several initiatives at FDA that have helped us to move this process forward, and then I am going to talk about in particular two initiatives, the Pediatric Rule and FDAMA, and I am going to briefly review what has been happening under each of those initiatives.

Finally, I am going to present the questions that we would like some feedback on.

[Slide.]

This is the list of currently approved indications in pediatric psychopharm. As you can see, it is a short list. We have three drugs that are specifically approved for pediatric OCD. The ADHD drugs, of course, have been approved for a long time. That is probably the best studied area in pediatric psychopharm. Halopericol and Pimozide are two drugs approved for Tourette's. Lithium is approved down

to I believe age 12 in mania. Imipramine is approved for bedwetting. Doxepin, another tricyclic, and this is very old labeling, is approved for something called psychoneurosis. This predated the present group by many years.

Finally, two antipsychotics, haloperidol and chlorpromazine, are approved for a variety of behavioral problems, everything ranging from agitation and aggression to hyperactivity. Again, these approvals occurred a very long time ago.

In any case, obviously, many of the disorders which are currently being treated in this area do not have approvals.

[Slide.]

Now, just a brief background on some of the initiatives that have occurred in recent years. Actually, this goes back about 20 years with the 1979 Pediatric Rule, which established the Pediatric Use Section in labeling, and then the 1994 Pediatric Rule, the 1998 Pediatric Rule, and then the 1997 FDA Modernization Act.

All of these initiatives were intended to stimulate research in pediatric indications generally. I am going to focus mostly on the last two, the 1998 Pediatric Rule and the FDA Modernization Act.

[Slide.]

Just briefly, the Pediatric Rule allows FDA to require pediatric studies under certain conditions. There are actually two parts of it, one part that refers to new drugs, and by that is meant not only new chemical entities, but also new indications for already approved drugs, new dosage forms, new dosing regimens, and new routes of administration.

The critical element for invoking this rule is that there is some pending application or an application is being considered for submission, and that allows us to have discussions with the company and require that they do studies in a pediatric population if it is felt to benefit the population.

There is another part of that rule referring to marketed drugs, which theoretically, would allow us to require studies even though there is not a pending application. That part of the rule has not been invoked to my understanding. So, the focus has been almost entirely on situations where an application is actually pending.

[Slide.]

Now, the other initiative actually occurred under this 1997 FDA Modernization Act. This again applies to both new and marketed drugs. Unlike the Pediatric Rule, which allows us to require studies, this is voluntary, and this encourages pediatric studies again when it is determined

that information from those studies would produce health benefits. It is not limited to approved indications. As I pointed out, it is voluntary.

The critical part of this law is that it allows for additional exclusivity to be given for doing those studies, and this additional exclusivity is applied to whatever existing exclusivity a drug may have or to whatever existing patent protection it might have, so this is a major financial incentive, and has resulted in a lot of activity in pediatrics generally.

[Slide.]

So, the bottom line is that FDA wants and can require pediatric studies for certain indications where there is deemed to be a need. The sponsors have a financial incentive under FDAMA to conduct pediatric studies, and so it behooves us to try and identify those indications where there would be a benefit from doing pediatric studies and, in addition, to work out the details of whatever might be needed to conduct those development programs.

[Slide.]

What I want to do next is to talk about what some of the results have been of these initiatives. Under FDAMA, we have issued written requests for three different indications, and these are the indications - major depressive disorder, obsessive compulsive disorder, and one

for generalized anxiety disorder.

Up until now there has been a total of nine written requests issued for these three different indications under FDAMA.

[Slide.]

In addition to FDAMA, we have invoked the Pediatric Rule in the following situations. Again, the situation that occurs here is that a company is coming in with an application. In most cases, it is a supplement for a new indication in adults, and it is our judgment that there is a need to look at pediatric populations. So, under the Pediatric Rule, we have required companies to do studies in these four different areas - posttraumatic stress disorder, social anxiety disorder, mania, and premenstrual dysphoric disorder. Obviously, the latter refers to adolescents.

[Slide.]

Now, there was one situation which actually we brought to this committee last November, and that was the question of whether or not, under FDAMA, we should issue a written request for a company that was developing a hypnotic, and the question was whether or not we should issue a written request to encourage the company to do pediatric studies with what is the usual claim for insomnia in adults.

It was discussed with this committee, and the consensus was that that would not be a good idea, so we did not issue a written request. Alternatively, the committee recommended that there may be one area that would benefit from further discussion and work, and that was the area of sleep phase deregulation in patients either in neonatal intensive care units or in pediatric intensive care units, an idea that had not developed to the point of justifying a written request, but something that ought to be explored.

[Slide.]

Now, there are several other areas where there is active consideration of either invoking the Pediatric Rule or issuing written requests, and these are the indications - schizophrenia, panic disorder, this entity known as conduct disorder, and then the question of ADHD in children less than 6.

This becomes an issue because, as you may well be aware, methylphenidate, which is, of course, approved for the ADHD, the current labeling indicates that it should not be given to children less than 6, and, of course, as you well know, there is a fair amount of use of methylphenidate and other stimulants in younger children.

So, the question is should FDA be asking companies to study new formulations of these products in younger children.

[Slide.]

Now, in terms of the written requests that we have already issued, these are the age cut-offs that we have established quite arbitrarily, you know, based on our discussions with various experts in the field. For major depressive disorder and OCD, we have cut it off at 7 years, for GAD, at 6.

[Slide.]

The question, of course, is what is the appropriate age cut-off for these various indications of interest in pediatric psychopharmacology.

[Slide.]

Now, I want to turn briefly to a paper that I believe was in your package. This was a paper that was published by Dr. Zito and her colleagues at the University of Maryland back in February. What it looks at is the prevalence of use of various psychotropic drugs in preschoolers that she was defining as age 2 to 4.

Basically the way this slide works is that we are talking per 1,000. So, if you think of a cohort of 1,000 patients, 4.1 out of that 1,000 in '91--she looked at several databases, this is from the Midwestern Medicaid database, and I am just giving you part of her data just to make a couple of points--so, we are looking at '91 to '95, and as you can see, the use of stimulants increased from

about 3-fold during that period of time, so that here, in '95, roughly 1 out of 100 preschoolers in that population were being prescribed a stimulant.

For antidepressants--and this includes both tricyclics and SSRIs--the use increased a little over 2-fold, from 1.4 to 3.2. Clonidine use increased dramatically from 0.1 up to 2.3, and the neuroleptics, although the use didn't change, it's 0.7 to 0.9, you still have roughly 1 out of 1,000 preschoolers in that cohort who are getting an antipsychotic.

[Slide.]

I think her data raised a number of questions. The most obvious one is what are the clinical entities that are being treated in that population of 2- to 4-year-olds and sort of a corollary to that, assuming that the stimulant use is for ADHD, a question might be is ADHD a meaningful diagnosis in these patients aged 2 to 4.

Another question that comes up, and this comes up in part with my discussions with various experts in this field, I have the impression that a lot of the use of other psychotropics in preschoolers is not focused specifically on diagnostic entities, but is focused more on certain behaviors, and so that is one question is how much of this use does represent the treatment of nonspecific symptoms rather than specific diagnostic entities. Then, a general

question is, is the absolute use and the increase in use of these drugs in this population justified.

[Slide.]

Now, I want to turn briefly to this question of focusing on nonspecific symptoms rather than specific diagnostic entities, and the question is would nonspecific symptoms, such as, for example, agitation or aggression, be considered acceptable targets for drug development programs in the pediatric population.

[Slide.]

Now, there is a precedent in FDA for approving drugs for nonspecific symptoms. Most of our approvals are for specific entities, such as, for example, something like pneumococcal pneumonia, rheumatoid arthritis, but obviously, we have approved drugs for nonspecific symptoms that cut across diagnosis, things like pain and fever. So, there is a precedent for doing that.

[Slide.]

Now, what I would like to do in this slide is to run through sort of the thought process that we go through when we are considering whether or not to even entertain the idea of looking at a nonspecific symptom as a target for an indication.

In general, we would like to have a universal definition for that symptom, in other words, whatever

diagnostic entity it is associated with, it should be defined in the same way, it should be measured in the same way. There should be some commonly accepted way of assessing and measuring that symptom.

Ideally, you would have a pathophysiologic understanding of that symptom. Again, from whatever context it arises, you would like that nonspecific part of it to have some understanding of it, again, so you can be confident that you are talking about the same thing from disease to disease.

It should be equally responsive to treatment regardless of the context in which it is occurring, and, in general, if we were going to consider approving a nonspecific claim, we would like it to be supported in several different disease models. For example, if you are going to approve an analgesic, you would look at it in several different pain models.

[Slide.]

Now, I am not going to spend a lot of time talking about safety. There was a good bit of discussion early on, on some of the problems of assessing safety in this younger population. Obviously, one is concerned about pediatric patients because of the fact that they are growing and developing, and are perceived as being more vulnerable to the effects of drugs.

There are not a lot of good preclinical models for predicting possible subtle developmental effects, nor are there even good clinical methods for assessing subtle developmental effects. We had again some discussion of that earlier. As you get into the preschool population, there is obviously the additional problem of even having difficulty because these younger patients don't verbalize very well, so it is very difficult to get at adverse effects in much younger patients.

[Slide.]

As Dianne mentioned, there is a lot of activity going on in the near term, in terms of looking at pediatric psychopharmacology. There is this conference, the Surgeon General's Conference next Monday, which is going to look more broadly at children's mental health. Part of that will focus on pediatric psychopharm.

NIMH is holding a workshop the following Monday on the problems in looking at long-term safety of psychotropics in children, and again there was some discussion of the problems in doing that earlier in this meeting.

On October 2nd and 3rd, we are holding a joint workshop with NIMH again to focus on the psychopharmacology of very young children, preschoolers.

Then, the American Academy of Child and Adolescent Psychiatry is having a workshop at its annual meeting later

in October. This is sort of a follow-on to the NIMH/FDA meeting, and the focus of this meeting is going to be to look at practical aspects of doing studies in preschoolers, you know, very practical things like how to make kids even comfortable participating in a clinical trial. So, there is a lot going on in the near term.

[Slide.]

These are the questions that we would like to have you think about. What additional psychiatric indications in the pediatric age group would benefit from psychotropic development programs? In particular, what should be the lower age limit that we should be looking at in considering these?

Again, in particular, what psychiatric diagnoses exist in the preschool population that would merit further work in terms of drug development programs?

Again, this question about whether or not nonspecific symptoms, such as agitation or aggression, would be targets that should be look at in drug development programs.

I think I will stop there. Thanks.

DR. CHESNEY: Thank you. Our next speaker is Dr. Richard Malone from the Eastern Pennsylvania Psychiatric Institute in Philadelphia. He will be speaking to us about pediatric psychopharmacology: a clinical perspective.

Pediatric Psychopharmacology: A Clinical Perspective

DR. MALONE: I would like to thank the committee for this opportunity to speak today. Most of my comments will really be directed towards preschoolers, and I think a lot of Dr. Laughren's were directed towards all children and adolescents.

[Slide.]

My first slide is similar to one of Dr. Laughren's. The prescription of psychotropic medications to children has always been somewhat controversial, at least from a societal point of view, and I think this includes both labeled and non-labeled usage, as well as some other usages like polypharmacy.

Dr. Zito's recent publication highlights some of the controversy that exists about prescribing medication in preschoolers. As was said previously, she had found in her study that usage had increased between 1991 and 1995 for stimulants, antidepressants, and clonidine.

Secondly, she found that the rate of neuroleptic use was somewhat stable over that period of time. I do know that we had another dataset that I looked at partly with Dr. Zito, where we found actually that the usage of the atypical antipsychotics had increased during that period of time, but I am not sure how that was related to this dataset.

Thirdly, she found that the less well established

agents increased at the greatest rate. I think all of these findings point towards the fact that we need--because most of this usage was off label--it points towards the fact that we need more well designed, preferably placebo-controlled studies to look at this usage.

Another comment I would like to make about her findings is that the fact that the less well-established agents increased at the greatest rate, I think to some degree shows us what promotion of medications can do that you can get newer medicines prescribed easily, and it also shows the willingness of clinicians to use even less well-established agents in their daily practice.

[Slide.]

Again these are the rates of prescription. The highest rate of prescription was for methylphenidate at 1.2 percent, and the other rates were all under 1 percent.

It is hard really to know what these medications were being used for, because the report did not include diagnoses, and I don't think there is a way that they can tie diagnoses in with drug use in her report. I think that Dr. Laughren was right that many usages are probably nonspecific although in my experience, I think most preschoolers who end up on medication have some form of hyperactivity than other comorbid conditions or symptoms including aggression and also severe developmental disorders

at times. So one I guess, if you had to guess, would think that many of these children might have a diagnosis of ADH.

In any case, I think we do need more psychoepidemiologic studies to try to figure out what exactly people are doing, studies that are designed to let you know what medications are being used and what they are being used for.

[Slide.]

Now, I think the main concern about using psychotropic medication in young children is really the safety issues. Young children's brains are still developing and we don't know how these drugs interact with the way their brain will develop.

Secondly, many of these children will end up on medication for a long-term period, and we don't know the long-term effects of most of these drugs.

[Slide.]

I think in young children there are several things to keep in mind. Past studies have shown that in a number of cases, young children have more serious side effects with medication.

The first medicine I have up here is lithium. In 1972, Campbell published an article about the use of lithium in a group of young children, and they were being treated mainly for aggressive behavior, but even in a small group of

children, there were a number of serious side effects. For instance, some neurologic side effects like dysarthria. EKG changes, various forms of heart block were found in a number of these children.

In another dataset, looking at lithium, actually in a somewhat older age group, it was found that the rate of side effects actually increased with decreasing age, again pointing out that younger children may have more side effects.

In the case of clomipramine, clomipramine had been an agent, and had been studied in a group of children and young adults with autism. It had been found to be a fairly effective agent in that particular study.

This study by Sanchez, et al., was a study in young children, preschoolers, and what they found was that they really didn't have any efficacy, but again they had a number of serious side effects including things like urinary retention and severe behavioral toxicity with the agent.

In both of these drugs, the side effects were found at therapeutic dosages, so it wasn't really just a matter of having high dosages of the drug causing side effects.

[Slide.]

The other point about young children that was partly shown in the clomipramine study is that behavioral

toxicity with psychotropic medication may be greater in younger children than it is in other age groups.

Haloperidol is probably one of the most critically studied treatments in autism, but if you look at the studies of haloperidol in autism, there are a number of behavioral side effects in some children including increased irritability.

Actually, in the developmentally disordered age group, apart from these studies, it just seems clinically that the rate of behavioral and other side effects seems to be increased with other agents besides haloperidol and clomipramine.

[Slide.]

In order to evaluate the side effects in young children carefully, I think it will be necessary to have placebo-controlled studies. In many well-designed studies of children using psychotropic medication, a significant number of children have side effects on placebo, so without a placebo control, it is going to be hard to estimate what the actual side effect profile would be with active drug.

[Slide.]

I think another thing to keep in mind clinically when designing studies of psychotropic medications in young children, is that careful baseline assessments will be needed and preferably at least two baseline assessment.

When you are talking about young children, they may react very differently the first time they come into a new setting, so you would want more than one baseline rating. Secondly, you are often separating young children from their mother or parent, again a new experience, and so their behavior may chance after one or two ratings just based on getting used to the setting.

There are a number of assessments that are available for efficacy studies, and I am more familiar with the assessments for studies in autism, but there are a number of assessments that have been used in studies over the years for efficacy, as well as safety.

[Slide.]

As has been said, there are very few medications that are labeled for young children. In fact, I think, by and large, it is only amphetamine and haloperidol that is labeled for children as young as 3 years old. Most other medications are labeled as not recommended for use. Therefore, it is pretty apparent that we do need careful, well-designed studies with controls, and we do need to have also adequate sample sizes to look at the safety and efficacy of these medications.

Another point I would like to make is that these studies should be done by investigators who are experienced with the population. I think this point had been made

earlier that it is more difficult to assess young children for efficacy and safety. Young children don't know how to present their complaints, and I think people who are used to rating even older children and adolescents don't always have the experience of rating young children for side effects.

[Slide.]

I was asked a little bit to comment on what disorders I might consider for studying in young children. These are a list of the disorders from the DSM IV with their prevalence rates. Many of these disorders are not present in young children particularly, but I think what you would want to consider in treating a young child with medication is that they would have a serious disorder if you are thinking of designing studies that has its own onset in early childhood, and I think in this list that the disorders that would come to mind are pervasive developmental disorder or autism, a disorder that often has severe behavioral symptoms and early onset.

I think many of the young children who end up being put on medications do have forms of mental retardation, but mental retardation alone is not an indication for medication, and in treating children with mental retardation, it is generally behavioral symptoms that people are looking at. However, most of those children also do have comorbid ADH, I think.

I think partly because the medications seem to be used probably most frequently in ADH and young children, it does call for study of that practice, particularly for the safety of that practice.

I think the other concern I would like to raise about doing pharmacologic studies children, young children age 2 to 4, is we have to be careful that--I don't know how to say this--kind of the research industry doesn't start using young children as a commodity, that we have to be very careful what we do with young children in studies.

Secondly, I think there has been a lot of concern about the use of psychotropics in young children as evidenced by everything that surrounded Dr. Zito's article, and I would think one concern you might have is if you begin labeling medications as appropriate for use in very young children, you might have this unintended effect of actually increasing the usage of medications in young children.

Those are the remarks I would like to make.

DR. CHESNEY: Thank you, Dr. Malone.

Dr. Mark Riddle from Johns Hopkins Medical Institution is going to speak to us about pediatric psychopharmacology: a research perspective.

Pediatric Psychopharmacology: A Research Perspective

[Slide.]

DR. RIDDLE: I appreciate this opportunity to

present to the committee.

[Slide.]

I am going to focus on 3- to 5-year-olds. Now, why 3- to 5-year-olds, and perhaps before that, why this breakdown. I don't think the breakdown I have here by ages fits necessarily the various age categories that the FDA uses. I think it is fairly close.

I have chosen it for a couple of reasons. I think in terms of clinical experience, the lowest that I am aware of most colleagues going in terms of age for prescribing psychotropics is about 3. If you look at Dr. Zito's data, which was for 2- to 4-year-olds, there were very few 2-year-olds in that sample. So, for clinical reasons and looking at her data, and also I think for developmental reasons in terms of being able to have any chance of assessing a child, I have chosen 3 to 5.

Now, why 5 is the upper limit? I think because many studies to date have gone to age 6 in kids, sometimes 7, but somewhere around 6 is what traditionally has been considered school age. It is also the age down to which many assessment instruments that are used in clinical research have been studies and validated, but this again is perhaps my parochial approach to this, but 3- to 5-year-olds.

[Slide.]

What about current ways of classifying or trying to come up with a diagnosis that one might study? Dr. Malone just talked about DSM, and I think offered an extensive list of potential diagnoses there, and I think you are all familiar with the DSM.

The other diagnostic sort of published diagnostic booklet that is available is one called "Diagnostic Classification 0 to 3," and it was published in 1994 by the National Center for Clinical Infant Programs. It unfortunately focuses primarily on younger kids, and I don't think it is perhaps at this point useful for the 3- to 5-year-old group, but it is something that is out there, and I think there is a group with expertise in thinking about diagnoses in quite young kids.

So, I think what most clinicians are left with, and perhaps researchers, too, is SOYP, and I don't mean to be cute, but it is sort of seat of your pants. Unfortunately, I think that is kind of where the field is right now diagnostically with 3- to 5-year-olds.

[Slide.]

What about current clinical practice? I think that although some of it is focused on the disorders that Dr. Malone listed, again, my impression--and this is not based on, I don't think there is any really good data particularly in this country--there is some European data,

sedation prn, and many of the drugs on the list that Dr. Zito had worked quite well as sedatives except for the stimulants; sedation ongoing, and behavioral disorganization, and the neuroleptics and the stimulants for that sort of broad category.

Now, this may be a bit of a cynical view, but I think part of the reason we really need research is I think this is what is going on currently, in part because there is not much out there to guide a clinician's practice.

[Slide.]

I am going to focus on what I think are, quote, "indications" for the under 6-year-old group. My colleagues and I published a paper in 1998 where I think we used the 1997 package inserts. We went through all the psychotropics in the PDR looking for anything that appeared to be an indication.

Dr. Laughren, I think I agree with you almost completely, maybe I have got something that is not quite right here, but I think that we have, not methylphenidate or Ritalin, but the amphetamine salts, marketed in this country now as Adderall, or dextroamphetamine are approved down to age 3, no data that I am aware of to support this other than we will talk about this in a bit, a few small studies.

I don't know if these were "grandfathered" in or whatever, but I don't think there is any support for this.

[Slide.]

Then, we have the neuroleptics. Again, I am not aware of any data to support this. What are described as severe behavior problems or short-term HA hyperactivity down to age 1 for chlorpromazine--that is thorazine, the original and quite sedating neuroleptic--and haloperidol, again exactly the same descriptors, behavioral problems and hyperactivity short term, but there is no age listed in the package insert. For haloperidol, for some reason it says should only be used after a non-neuroleptic has been tried.

I listed thioridazine, and I don't know if this is correct. This is Mellaril. I think it was there in '97. It is not in the '98 PDR, and there is now a "black box" because of concerns about Q-T prolongation, so perhaps it is not going to be used much, but at least chlorpromazine and haloperidol may help with that disorganization and are quite good sedatives.

[Slide.]

Dr. Laughren, this is the one I am most concerned about, and I may be misreading this. If you look at the package insert, it lists three indications for diazepam (Valium): anxiety, muscle spasm, and adjunct anticonvulsant. Later, without saying which indication this is for, it just says "indicated in use down to age 6 months." Again, perhaps that is just for anticonvulsant

use, but you wouldn't know that by reading the package insert.

[Slide.]

Other commonly used drugs, three of which weren't part of Dr. Zito's study, but I think are used fairly commonly in this age group, are diphenhydramine and hydroxyzine, again terrific sedatives, clonidine and phenobarbital. Not much good data on this, but I think this is where the prescribing is.

[Slide.]

Now, what symptoms or disorders may be medication responsive? I don't think anyone has a good answer to that. I wish I could give you a research perspective, but I don't think that currently there is much in the way of solid believable data, because it is an area that just hasn't been studied much.

I think the only area where we do have some small controlled studies are for hyperactivity, impulsivity, and distractibility, the core features of ADHD.

I have listed a couple of others here that I think we see in 3- to 5-year-olds, symptoms or problems that we see, that I think may be medication responsive. These don't fit so neatly with your DSM diagnoses, but aggression, that Dr. Laughren mentioned, behavioral disorganization, I had this in the slide, out of the slide, in the slide, out of

the slide, I am not sure, but I think we see a fair number of kids, if you go into a therapeutic nursery, and talk to the teachers, and the youngsters are having a lot of difficulty with, several youngsters, sometimes, it's, well, this looks like ADHD to me, but other times he is just so disorganized, he is all over the place. Is this psychotic, pre-psychotic, quasi-psychotic, what is it?

I think the neuroleptics are used a lot for this. Also, Dr. Malone mentioned autism, pervasive developmental disorders, mental retardation. Well, obviously, any of these can occur in youngsters with any of those diagnoses, and I think particularly amongst those with developmental disabilities, this behavioral disorganization may be something that is ill defined, but is treated a fair amount with low-dose neuroleptics.

Then, I think in some youngsters there is fairly severe anxiety that one can tease out, and it perhaps may be responsive to medication, and in some, mood lability.

I don't think this is a definitive list. I don't think this is one that the research community would necessarily agree upon. It is sort of my best first pass.

[Slide.]

What about controlled psychotropic data to support any of this? I mentioned before, for ADHD, there are several studies of methylphenidate (small n), results

suggestive of the medication being more helpful than placebo for impulsivity, distractibility, hyperactivity, and that is all that I am aware of in the 3 to 5 population for any "psychiatric" problem.

By the way, I have all these slides on a one-page handout.

[Slide.]

Now, can symptom severity be assessed in 3- to 5-year-olds? Again, I will give you my take on that. Here, I have broken it down into three groups, what I would call "external" symptoms, in other words, symptoms that we could assess by looking at the child, not asking questions, not asking for tell me about your internal distress, but let me observe, watch, and I can assess it - activity, distractibility, impulsivity.

I don't think this study has been mentioned, but the NIMH has just funded a six-site study to compare placebo and methylphenidate in preschoolers with ADHD. There is going to be a 12-week psychosocial treatment that will precede the medication to try to not study kids that respond to psychosocial treatment.

For that study, parent report, teacher report, and then a simulated classroom observation are going to be the primary measures. I put a question mark next to the simulated classroom. There is, I think, enough experience

and enough data to indicate that for older youngsters, the school age kids, the 6- to 12-year-olds, that a simulated classroom can work quite well for obtaining excellent observational data.

There isn't much in the way of data in 3- to 5-year-olds, and we are going to be learning as we go here in part, in this study.

[Slide.]

The behavioral disorganization I have listed here as both external and internal. One can observe this again in the home or the therapeutic nursery, and with some articulate, say, 4- or 5-year-olds, you may be able to tell from their speech something about thought disorganization. That is not always so easy to do.

Again, parent report, teacher report, and here, expert clinician assessment, and I have a question mark because I don't think this has been adequately studied.

[Slide.]

Finally, anxiety or mood difficulties, internal symptoms primarily, and here, parent report, I think that that may work reasonably well for some aspects of anxiety, clinging, avoiding, difficulty separating, separation anxiety, et cetera, so for some things, I think that is the case, or fears, unrealistic fears.

For other symptoms, you know, do you feel

depressed? Huh? I mean we don't expect 3- to 5-year-olds to be able to answer that question so well. Or are you anxious today? That sort of ability to be self-observant and to be able to report obviously is not very far along in terms of maturation.

So, that is why again I have the question mark next to expert clinician assessment, can we do it, and it hasn't been done I don't think enough yet to say that we have the research instruments.

[Slide.]

Recommendations. Again, this is a little cute, but I thought with preschoolers, it's Stop, Look, Listen, and then if it's everything is okay, go.

So, what I have with Stop, and I guess it's not really stop, but I am concerned about the unsupported indications. Maybe I am just being a bit fussy, but I don't think it's a service to preschool kids or clinicians to have any of these "indications" in the package inserts since there is no data to support them.

Look at the PATS experience, the Preschool ADHD Treatment Study. I hope that we will learn something from this study over the next few years. The study is just about to start. I think enrollment will start over the next month, and will continue for a couple of years.

I think that this is going to be a learning

experience for all of us. There are six sites involved, and hopefully, we will gain some useful information, not only about is methylphenidate effective, but what are we doing right and what aren't we doing right in terms of conducting treatment studies in kids this age.

Listen to more expert opinions. Well, clearly, the agenda for the next couple of months, that Dr. Laughren had suggested that you all are doing that, which I think is terrific, and then finally, Go for more research. Obviously, anyone I think interested in young kids and these disorders would push for that since the prescribing is happening, the treatment is happening, and it is based on almost no data.

Thank you.

DR. CHESNEY: Thank you very much, Dr. Riddle.

Now, Dr. Vitiello, who is Chief of CATPIRB, DISR at the NIMH, is going to review the NIMH perspective on pediatric psychopharmacology.

NIMH Perspective on Pediatric Psychopharmacology

DR. VITIELLO: I am with the Trial Treatment Branch at the NIMH. That is the acronym, but it is much more complicated.

[Slide.]

Just a few comments from our perspective. Historically, NIMH has played a major role in the

development of any research in pediatric psychopharmacology, pediatric psychopharmacology in general, meaning in subjects under age 18.

Actually, until very recently, NIMH has been the only source, the main and only source of support for most pediatric psychopharmacology, so that all the studies on stimulants, on tricylics, for instance, a little bit there has been done on clonidine, has been done under the support of NIMH.

Only recently, thanks to new legislation and new rules that have been introduced in the last three or four years, the industry has become interested in this, and we are seeing actually a change, and we are already redirecting our efforts, so we don't plan to do as much placebo control, short-term studies just to show efficacy and safety on the short term or pharmacokinetics studies as we have done in the past, because we know that the industry will be probably interested in doing that, and we will focus our attention on other questions that are relevant to the clinicians, such as what is the long-term effects of treatments, long-term safety, or how does pharmacological treatment compare to a psychotherapeutic treatment, or is there additive advantage in combining pharmacological and psychotherapeutic treatment.

So, these are all questions that we are moving to

address, or the issue of comorbidity that typically is not addressed in the typical industry-supported studies.

Anyway, since the theme of this meeting is mainly on very young children, preschoolers, I have to say very clearly that the study that Dr. Riddle mentioned, which is the preschoolers with attention deficit disorder treatment study, the PATS, that is starting now, is the only and first study that we have in our portfolio that we have started so far.

We haven't had any opportunity to study any psychotropics in preschool age previously. We have preventive intervention, we have psychotherapeutic intervention, but not pharmacological intervention. Even in the studies with autism, typically, the age of our protocol start at about 5, because for that, the instruments, the assessments, and the outcome measures have not just proven to be sensitive enough to detect treatment effects.

But all said, which is the very essential communication about preschoolers, I mean this is a new area for us, and we are looking very much forward to the October 2nd meeting to get some directions in this are. I want to give you a perspective of what the psychopharmacology program is at NIMH.

[Slide.]

The main research question that we have, that

relates to treatment, relates to all the aspects that the clinician would like to know about the treatment, that is not limited to is it better that placebo, but how does it compare with other treatment, and is it safe, and for which patient it is indicated, and what are the moderators of treatment, and so forth.

Our mission, of course, is not to register drugs or to get an indication. Our researchers' primary goal is to answer a clinical dilemma that practitioners are currently struggling with. Each time that there is a clinical dilemma, and there is a methodology for addressing that dilemma, we are interested in the clinical trial. So, that has been really our policy.

[Slide.]

The branch where I operate addresses treatment and preventive intervention in general, and I think this is a very good thing, because we don't see psychopharmacology as something isolated, but something that is to be integrated into other treatments or preventive interventions that are available for children and for families.

As you can see, roughly half of the budget in '99 was devoted to treatment, and the remaining 45 percent is to preventive intervention.

[Slide.]

If we look at the pie of treatment, you will see

that psychopharm, pure psychopharm meaning to test only treatment that relate to psychopharm, the percentage is about one-third. One-third of the budget for treatment goes--I am sorry--a little less than one-third or one-fourth actually goes to psychopharm, one-third goes to psychosocial treatment, which is psychotherapy, and a larger portion that actually is growing in 2000 will be much bigger, goes to combined treatment.

Combined treatment is a category that includes clinical trials that compare either psychosocial to a pharmacological intervention, or they compare combined treatment, psychosocial plus pharmacotherapy compared to a control, whatever it is. It could be the single treatment in isolation, or a placebo, or something else.

So, basically, we are moving into looking at, comparing the effects of different treatment modalities.

[Slide.]

Granted that a substantial amount of money, millions go to prevention, and we look here at treatment. Again, this is what the pie in the previous slides basically summarized, that psychopharm is not the area where we put most of the money, and this is not really done a priori, this basically reflects the applications that are sent to us from university and researchers, that seems to be more interested in studying the combined treatment and

psychosocial treatment than straight psychopharmacological studies.

[Slide.]

If we look at the indication, the clinical entities that get funding for treatment studies, you see that depression, this is 8 million per year that goes to support clinical trials in depression, followed by anxiety, attention deficit disorder, and autism.

[Slide.]

One of the initiatives that was launched about four years ago has been the network of a research unit on pediatric psychopharmacology in order to provide a structure, an infrastructure where clinical trials in pediatrics could be conducted on children with mental health disorders, that could be used either by NIMH, by industry, or by private foundations.

[Slide.]

This is a network of research that are devoted to multi-site clinical trials in children.

[Slide.]

The units are based at academic research settings, and the main focus is to study the efficacy and safety of psychotropics that are commonly used in the community, but without adequate data.

[Slide.]

Again, it was established about four years ago through competitive contracts with NIMH.

[Slide.]

At the moment, there are seven RUPPs. Some of them have subcontracts, like Columbia has subcontract to NYU, Ohio State to Kennedy Krieger.

[Slide.]

There are experts in child psychiatry, psychopharmacology, pediatrics, clinical trial design methods experts.

[Slide.]

There is a data management center that is separate.

[Slide.]

And there is a statistician also that provides support, and it is available for industry, for NIH, for any private foundation who wants to support these studies.

[Slide.]

What NIMH does with this RUPPs is to support the basic infrastructure, and then protocols that are of public importance, not funded or unlikely to be funded through grant mechanism, and not sponsored by industry.

[Slide.]

This is an example of multi-site protocols. The first one is a double-blind study comparing flavoxamine and

placebo in children with anxiety disorder. It is a study that was completed, and it has been submitted for publication. It was the first double-blind study of an SSRI in children with anxiety disorder out of their OCD.

This protocol is in progress now, has randomized about 75 subjects, is to study risperidone for children with autism and behavioral disturbances, such as aggression, agitation, and then there is also a study on SSRI for children who are depressed and also suffer from bipolar disorder.

These are just examples of some studies.

[Slide.]

Another example of a study, the treatment of adolescents with depression study.

[Slide.]

The study basically compares the effectiveness of different treatment arms and different modalities. One treatment arm is fluoxetine, which is the medication-only study, treatment arm. Then, we have CBT, COMB (?) therapy, which is a specific psychotherapy for depression, a combination of the two, so patients randomized to COMB receive both, and then placebo only. So, this study basically will inform about the relative efficacy of modalities like pharmacotherapy and psychotherapy, and the potential value of combining the two treatments together.

[Slide.]

The projected sample size is 432. The study has just started. We have randomized about 30 subjects at the moment. It is a parallel group design.

[Slide.]

Different stages. There is an acute treatment, consolidation, maintenance, and one year open follow-up. It is set up to answer multiple questions at different stages.

[Slide.]

These are recently funded studies through grants that are either starting now or will be starting in the next few months. Just to give you an idea of what is in the pipeline basically.

One is a study to evaluate the value of continuing antidepressants in adolescents who have improved, were treated because of depression and have improved on the antidepressant. Basically, it is aimed to answer a question: after six months of treatment of adolescent major depression, is it a good idea to discontinue treatment or you run the risk of increasing the relapse rate?

This study is run at the University of Texas, Dallas, and the PI, Graham Amsley, will address that question. The study has started, but I don't know how many patients have been enrolled so far.

So, basically, it is stabilization for six months

and then randomization either to placebo or to continuing medication. The medication in question is fluoxetine (Prozac).

Another study is the treatment of SSRI-resistant depression in adolescents. Now, there are couple of studies, one, NIMH supported, the other industry supported, who basically have shown that SSRI, such as fluoxetine or paroxetine, are better than placebo in the short term, however, there is still about 40 percent of adolescents who do not respond well to this medication, so the resistance to SSRI is very common.

So, the question is what to do with adolescents who do not respond to a first trial with an SSRI, is it worthwhile to give a second trial of another SSRI, or is it worthwhile to switch to a different entity, which in this case will be venlafaxine, or is it worthwhile to combine pharmacotherapy with psychotherapy.

So, there are different treatment arms in this study that will test this hypothesis. The sample size is going to be about 400.

[Slide.]

Another study that is starting is a straight placebo-controlled efficacy trial of valproic acid or lithium in youths with bipolar disorder, bipolar type 1. This would be the first--actually, Dr. Geller has already

done one placebo-controlled study, but this would be the first multi-site study that will test in a placebo control fashion the efficacy of mood stabilizers in youths.

[Slide.]

The last one is the study that Dr. Riddle has mentioned, which is an efficacy and safety of Ritalin in preschoolers with attention deficit disorder.

[Slide.]

I can just give you the basics about this study. Basically, there will be two groups of patients, age 3 to 5, which is the preschoolers, and the group 6 to 8, to contrast the ages. The preschoolers will be 198, the sample size, and 66 will be the school age.

There will be a period of screening and evaluation to make sure the diagnosis is correct, that there is no spontaneous improvement, that behavioral intervention alone that will be delivered during this period will not already trigger improvement, so that a pharmacological trial will not be justified.

It is to make sure really that these children really deserve a trial of medication. You know, we want to be very careful that we don't expose children who can be managed in other ways to medication.

There will be an open titration to explore a whole range of doses to make sure that the doses are tolerated

well, and there will be a placebo-controlled trial to see if methylphenidate is indeed better than placebo and is well tolerated in a controlled fashion, an open maintenance for patients who improve, and then a blinded discontinuation event of these 12 months to see if continuing treatment is appropriate and still is associated with improvement.

[Slide.]

Some areas where still we don't have enough research--I am not talking about preschoolers here, young children--I am talking about across the board, you know, areas where we need basically new protocols and new ideas, basically psychosis and schizophrenia in particular, still bipolar because it is under-represented in our portfolio, depression in prepubertal children--we get very little really under age 12, there is only one-half of a controlled study on kids with major depression who are in prepubertal age--autism, and conditions with comorbidity.

Also, we are encouraging researchers to look at safety issues. I think that particularly for preschoolers this is of paramount importance. All the questions that we receive basically from the lay public and practitioners that relate to young children have to do more with safety than with efficacy, and the basic question that goes in their mind is this basically - is it a good idea to expose for a prolonged period of time a child whose brain is going

through dramatic changes, to an agent who we know is psychotropic.

That is a very good question to ask, a very difficult question to answer, but in some way, it is not specific to psychopharmacology, it is not specific to mental health, because a lot of drugs that are used in pediatrics are steroids, other drugs that are used for known CNS, known mental health reasons have an effect on the brain, and so in some way, that question can be asked to any entity that is administered to children at a young age.

So, that is my comment about safety. The other comment about efficacy, when we go to very young children, that occurred to me during the presentation by Dr. Malone and Dr. Mark Riddle, that it is good to focus on symptoms, but since we don't know very much what the predictive value of symptoms are, not always we know the predictive value of symptoms at this age, probably we are better off if we focus really on impairment, on functional impairment.

You know, the child is aggressive or agitated or moves around and doesn't pay attention, it is not quite as important as the fact that because of these symptoms, he is not able to attend the preschool, is not able to play with other children, has no friends, is delayed in his interpersonal and social skills development, and so any treatment modality that we are testing in some way, we want

that is effective not only in reducing the symptoms, but in improving the functional outcome that should be impaired at the very beginning for the child to participate into a study.

So, these are the kind of ideas that I think will be part of the October 2nd meeting to which very much we are looking forward to.

Thank you.

DR. CHESNEY: Thank you very much.

Are there questions of the subcommittee members or any of the other speakers for the speakers before we go on to the questions the FDA has given us?

DR. SPIELBERG: A couple of questions about biology which we really haven't dealt with much today. We are talking about sort of prevalence of symptoms in children, often very ill defined.

You know, if you assume that the adult population, X percentage of adults have schizophrenia, and then some percentage of those have a series of different genes associated although we are far from understanding all of those, you have to assume that that same percentage of children, in fact, have those genes present, but that the diseases are not manifested at least as they are in the standard adult DSM classifications of the disease.

The issue of prevention came up, and I know there

is discussions about, you know, could you, in fact, prevent the first psychotic break by a pharmacologic intervention, these kinds of things.

To deal with any of those things, I think we are going to need a heck of a lot more biology superimposed on those kids, you know, what is autism. I don't know what autism is. It is a series of symptoms like schizophrenia right now is a series of symptoms that we work on.

As the biology is beginning to creep in, I think that is going to help us immensely because, after all, the drugs are directed against biologic targets. We are spending all of our time cloning receptors that supposedly are associated with either symptom reduction or hopefully getting at the etiology of the diseases, and yet, we know that those genes that are represented in adult diseases are present in kids not yet manifest, but maybe manifest in ways that we are ignorant of actually being able to pick up at that point.

Maybe we should be using more drug, maybe we should be using less drug, maybe we should be using different drugs that we are currently using in classifications of kids, and I hope that at the discussion we have, we can, in fact, get some much more broad insight into biology, because if we are to make any judgments about whether a drug should or shouldn't be used, it is going to

be understanding the underpinnings of the behavior for which these drugs are being used in kids.

DR. CHESNEY: As usual, you articulate it much better than I ever could, but I wondered about genetics of some of these diseases. For example, is a bipolar depression in a 3- to 5-year-old--and I was talking to Dr. Geller about this--the same as non-bipolar depression in a 3- to 5-year-old, and would they respond differently, and if we had a wrongly selected group of children, would we not show efficacy when it was there, and I am not even knowing exactly how to word the issue, but, Dr. Riddle, maybe you could comment on what we are trying to say.

DR. RIDDLE: Well, I think as you have articulated it, and as you know for most of our psychiatric diagnoses, we rely on phenomenology. Unfortunately, we have very little more than that to go on.

For some of the disorders, we are beginning to have some pathophysiology, although it is still somewhat primitive, but I think that is moving along.

Also, for some of the disorders, we have family studies that point to familiality and maybe segregation analyses that might point to a particular mode of transmission, but at this point we don't have much in the way of identified genes. I think that you know that

This is very anecdotal, but if I think about

bipolar disorder, I have treated two youngsters under age 6, and in both of those youngsters, one of the parents had fairly severe bipolar disorder, and the other one had fairly severe recurrent major depressions.

One of the questions--again, this is anecdotal--that that raises, are the youngsters with earlier onset just having more genetic loading, at least for some of the disorders. One could think about that for depression, bipolar disorder, some types of anxiety, et cetera.

But to come back to where I started, I think even for the school age kids and the adolescents, it is mostly phenomenology.

DR. CHESNEY: If I could ask one more question. Dr. Vitiello, you said right at the end that maybe we should be focusing on functional impairment, and I guess maybe that is all we have, but it reminds me of treating fever without figuring out what causes the fever, and maybe that is what we have to do at this point in time.

DR. VITIELLO: Well, I don't know about fever, but basically, what I was going to invite researchers not to limit their attention to symptoms, but to go above and beyond that, not to ignore symptoms, but to link symptoms to functional impairment.

After all, for fever, we have--just to go back to that example that you brought up--we have a threshold to

define what fever is. For issues such as aggression, agitation, hyperactivity, inattention, we don't really have a clear-cut threshold particularly for preschoolers.

For school age, maybe there are some norms, but still are norms. You know, there is not that clear cut-off that you have with a situation like fever. So, I think it is essential to focus on what is the impairment of a child, and to expect that whatever treatment we deem effective, that impairment is reversed.

I wouldn't be satisfied just if the symptoms disappeared if I don't have proof that the child will be better off.

DR. CHESNEY: Thank you.

Dr. Riddle.

DR. RIDDLE: Just to follow that up, in the anxiety study that Dr. Vitiello had mentioned, that was just completed, for that study the primary outcome variable included a combination of what we might consider the symptoms, how much internal distress was the youngster experiencing from the anxiety, and also how much were the physical symptoms of anxiety bothering the youngster, so what we would think of classically as symptoms.

But it also included how much problem was the anxiety causing in terms of avoiding things, activities, et cetera, how much problem was it causing in school, and how

much problem was it causing at home and other settings.

So, I think our studies, at least with the older youngsters, are beginning to include impairment in the assessments, although in a fairly primitive way.

DR. CHESNEY: Yes.

DR. RYAN: I wanted to just sort of reemphasize I think what Dr. Laughren put on the table for us, because I thought that organized at least my thinking well when you talked about the pluses and minuses of targeting symptoms rather than syndromes.

I think impairment sort of fits in there where, as I understood what he was saying, the main ideas were that the symptom had to be in common across a range of disorders, not simply a proxy for the disorder, and that hopefully it is targeted by the treatment in all of the disorders, not simply in one, and that, God willing, you have some idea on the mechanism that it targets. I think that everybody including Dr. Laughren, would flex on that one a little bit.

I have to say that I was less clear where the impairment fit in, because impairment, obviously, I think in psychiatry, we have learned to use impairment as a threshold criteria to say that the syndrome is significant enough that you want to treat the stupid thing, you know, that it is not simply deminimus or trivial or something and will get better easily, but I don't see mechanisms where I would say you are

particularly targeting impairment rather than using the impairment as a threshold.

Similarly, you are possibly accepting the sleep disturbance, it was less clear to me if there were even other symptoms right now, that my particular choice of guesses would be that the symptom is ready to target, and it is a little tougher to know on the aggression one. I think that is the interesting one, or at least one of the interesting ones that you put on the table.

DR. CHESNEY: Dr. Gorman.

DR. GORMAN: I would like to ask any member of the panel that just presented, in the PATS study that several of you mentioned, how are you comfortable that you are enrolling people with ADHD, and then why can't that methodology be generalized to other disorders.

DR. VITIELLO: Mark, it is your call. You are one of the PIs, so I think it is appropriate that you address it.

DR. RIDDLE: That is a very good question, and it is a question that I think every group that has looked at this protocol has raised. There clearly is no gold standard, and the critique we often hear is, well, we expect 3- and 4- and 5-year-olds to be active, they are fairly impulsive, and we don't expect them to stay sort of focused and sit in the chair doing spelling problems for 45 minutes.

So, the sort of "boys will be boys" argument is one that is throw up at us again and again. Now, how to deal with it, what we have tried to do is to use an instrument that was normed, so that we could say, look, here is what the population of kids this age look like, here are the sorts of scores they get.

To get into our study, the kids are going to have to be out here with the score. Another is to rely some on expert experience, and that is always a bit scary, but I think we have to do that.

The other is to have clear impairment and agreement across settings, settings like home, school, et cetera, and we don't know how to do it any better than that, and I think that a tough critic would still say, you know, that is kind of weak, but that is the best we have.

DR. GORMAN: I guess being a sort of wishy-washy critic, I assume you are talking about some sort of Connor derivative for the scoring system you are using.

DR. RIDDLE: Right, something of that nature, a parent and teacher report, although, as I said, we are going to use the simulated classroom.

DR. GORMAN: I guess the question I am asking then is that I think is, compared to some of the other methodologies I have seen in the mental health area, very rigorous. Is not a similar program underway to create a

criteria for autism, for instance, where this much language disability, this much behavioral disability, not functioning in settings at home and at school, why is that methodology so hard to generalize in the mental health field?

DR. RIDDLE: Ben, do you want to do the autism one?

DR. VITIELLO: It seems to me that the problem with autism is not the diagnosis, because you can make a diagnosis at age 2 with good validity, and so forth, is that we don't really know enough about the pathogenesis of the disorder to come up with a rational drug development program, and so far there hasn't been, as far as I know, any good candidates that is worthwhile testing in clinical trials.

There have been clinical trials, of course, but without very strong rationale for doing that, so that is really the reason why we don't see more pharmacological development in clinical trials in this age.

DR. CHESNEY: Dr. Geller.

DR. GELLER: Just going back to the question of why it can't be generalized, Keith Connor developed the scale for hyperactivity many decades ago, and although it has been tweaked, it has really never been bettered or surpassed or anything used instead of it, it works just fine, because hyperactivity is extremely easy to measure.

You can measure it reliably.

The question of threshold of what is impairment is very important because I think in one of the recent epidemiological studies, 63 percent of children who had skipped a grade were on Ritalin because, in that particular school setting, they were considered hyperactive, so threshold is really very crucial also.

When it gets to illnesses like autism and mood disorders, we don't have a Connor scale that pinpoints it reliably and in an easy 10-item way. There are very reliable and valid scales used in various kinds of research studies, but nothing that has the simplicity and ease of use and brevity of the Connor's.

DR. GORMAN: I guess I am still struggling. If I took five mental health professionals and put them in a room to examine one child sequentially, and the child had autism, whatever that is, would they all make the same diagnosis, and if so, would they use the same criteria? And if they used the same criteria, why aren't you comfortable telling me that is the gold standard?

DR. GELLER: If you did it and had five clinicians, I think you might come up with five different diagnoses. One would see just the hyperactive component and have the child on Ritalin, one would see the psychosis, and one would see the language and send the children for LD.

Like many large universities with a referral center, and when we get the charts of kids referred to us, that is usually what it looks like depending on the professional they were seeing, that is the diagnosis they have gotten.

I think it will help to keep in mind what I frequently say to parents when I am doing an informing interview, which is I start by telling them psychiatry is 500 years behind other medical specialties, and it goes back to all these comments about biology.

We don't have an x-ray, biological peripheral marker, a genetic marker or any other kind of method except phenomenology, we can interview, and if you are interviewing for something relatively straightforward like hyperactivity, you can get a lot of agreement. It is not so easy to interview for which language impairment. It's because the child is bipolar, which is because they have a loose association and they are schizophrenic, which is because they have congenital aphasia, and which is because they have the autistic impairment.

I think until we have more biology--I think that comment is really very, very key--we are going to continue to have difficulties developing interview scales that are any better than the ones we have with the exception in the preschool realm there is newer work.

John Looby (?) at my facility and other investigators around the country are looking for methods of looking at mood disorders in children, but I think nothing will be a big enough gain until we have more of the biology.

DR. RIDDLE: I think I would generally agree with Dr. Geller, but I think if you had sort of five clinicians--there may be a lot of disagreement--I think if you had five clinicians that worked with kids with developmental disabilities, or who were researchers in the autism area, there would be quite high agreement, and I think that most of them now doing research would use one instrument and actually could come to a diagnosis that everyone would say yeah fairly independently.

But if you go out into the community at large, no, but I think that the research for some of these disorders can be done based on the phenomenology, I guess that is the point I want to make. I don't want to come away from this with too much negativity.

DR. GORMAN: I guess I feel that, you know, a lot of symptoms, well, tuberculosis perhaps, we spent 300 years trying to figure out was a single disease, with syphilis perhaps an equal number of times, but at some point you have to define a diagnosis before you can move forward, and I think if that is the holding up point, then, in terms of starting research programs into either psychopharmacology or

psychotherapy or any other combined modality that you choose, then, you should become rapidly more comfortable with a diagnostic entity even if it's very exclusive.

If you want to use the Connor scale and say that you have to be over the 90th percentile to be ADD, you are going to exclude a lot of children who have ADD, but you still have a diagnosis.

I am guess I am curious as to why that hasn't progressed more rapidly.

DR. MALONE: I work in autism, and I think what Dr. Riddle said is true, if you get experienced clinicians, and you put five of them in the room, that you would have high agreement on the diagnosis, and there are a number of instrument that are used in autism that are fairly reliable for rating symptoms and making diagnoses.

I have had the same experience, for instance, in asthma. My son has asthma. I think we had to go to about three doctors before we got any diagnosis. I could ask the same question, you know, what is this asthma thing, but I think it really depends on the experience of the clinicians.

DR. CHESNEY: Yes.

DR. RYAN: I want to sneak up on the question in a different way or I want to combine two of them, which is that if these disorders, which is looking like a lot of them are, are complex genetic disorders, probably with a bunch of

genes, you know, the 8 to 15, not the 3 or 4, and they are genes all of small effect, you know, heritability under 2, and they are distributed frequently in the population, you just have to have an infelicitous combination of them that adds up and gives you, you know, maybe like a hypertension equivalent. I think it explains a lot of the complexity, but there certainly are biologic findings.

There is not a biologic finding that is diagnostic. Well, there certainly are psychological symptoms. Again, it is harder to make a test that says yes, you have got it, or no, you don't, because they are probably--probably many of them complex sort of additive disorders there. That is what you are trying to study.

DR. CHESNEY: Actually, one very positive thing that occurs to me is that by doing well controlled and rigorous studies, we may be able to sort some of this out. There may be populations of children that respond dramatically and others that don't, and because they are in very well supervised trials, we can maybe sort some of that out.

Subcommittee Discussion of Questions/Issues

DR. CHESNEY: Maybe we should go on to the questions. Dr. Murphy, do you want to elaborate on these at all or should we just go at them as written?

DR. MURPHY: You are having such a great

discussion, just go at them.

DR. CHESNEY: Well, the first one, what additional psychiatric indications in the pediatric age group would benefit from psychotropic development programs, and what ages should be included?

By "additional," do you mean other than everything we have discussed here?

DR. LAUGHREN: Let me paraphrase the question a little bit. Basically, what I am asking is how are we doing in terms of our application of the Pediatric Rule and FDAMA in terms of where we have been either encouraging or requiring studies. You saw the list. Is that about right or are there areas that we have been ignoring that we should be looking at, have we gone too far in some areas, and in particular, what about the age cut-offs, is that about right for the disorders that we have targeted or should we be looking at different age ranges?

DR. CHESNEY: Can we include our speakers having suggestions, so it is not just the subcommittee? So, if any of the speakers have suggestions, please go ahead and volunteer.

Dr. Riddle.

DR. RIDDLE: I don't know if you have the authority to do this, but I am concerned that some negative studies may not be published, that the company is required

to do the study, does it, there is no effect, they have gotten their six months' exclusivity, done deal, and we really need that negative data out there. I don't know what the deal is on that.

DR. MURPHY: The deal is that if they have negative results and we think it is a relevant, real negative result, it will go in the label. That is the point of exclusivity, it clearly says that when we asked for the studies, that even if they are negative, and particularly if there is a safety issue or an adverse event, that information will become available in the label.

DR. RIDDLE: Just one other comment or question. The difference between ages 6 and 7, I am not sure I understand what that is about.

DR. LAUGHREN: It is purely arbitrary. It is based on discussions we had at the time with various people in the field about where we thought we ought to cut it, but that is a question for you, again, in regard to the younger populations, it sounds to me from what you are saying that there is not much rationale for going much below those ages in terms of these diagnostic entities.

DR. RIDDLE: Yes, I would agree. I think down to 6 or 7 generally, for the disorders that you have looked at or are planning to look at, I think we can make a diagnosis, can get a reasonable assessment, and kids may benefit from

the medicine, 6 or 7, who knows.

Below that, maybe--maybe for ADHD, I think that is what I would say, maybe, and perhaps we need to see what happens with this NIMH study first.

DR. LAUGHREN: I am glad you offer that because that was going to be my next question, because we do have the authority at this point under the Pediatric Rule as new formulations of methylphenidate and other stimulants come along to require companies to go below that age, but if the feeling is that we ought to wait and see, that is fine, too.

DR. RIDDLE: One more here and I will stop. It does seem to me that you are between the rock and the hard spot, that the field that may not be mature enough to permit the studies, on the one hand, on the other hand, there is so much willy-nilly or a fair amount of willy-nilly prescribing going on that it is painful to sit and wait, and not have data.

DR. MURPHY: One of the things that we can do under the rule is we can defer studies. We have an option of not waiving them. However, we are then in the quandary of to defer studies, we have to come up with the best estimate of when we think we are going to ask for those studies to be done, and sometimes that is very clear, you are waiting for additional data either in an older age group or in an adult or some other process that is more delineated

than what we have here.

I think what Tom was saying is we could--was your comment that we should say until we get more information from the ongoing study, we should defer. We could come up with some estimates of what that would be, any further studies in the younger age group.

DR. RIDDLE: Ben, maybe you can help me on this, but if we took ADHD, for example, I would think that in three years, the data collection for at least the acute phase of that study will be complete and we will know something about was the study reasonable successful at recruitment assessment measuring change.

If the answer is yes, we are having some longer acting preparations coming on the market for both methylphenidate and amphetamine, and I think that they are going to be very attractive because of their convenience.

The study that NIMH is funding is short-acting methylphenidate. It's a place to start. I don't know, three years is a very long time, but something like that, it seems to me, would not be unreasonable.

DR. CHESNEY: Dr. Nelson.

DR. NELSON: This is not an area I know much about, but I guess the question is, is there any dose response data at least in older children where you can make a diagnostic classification with any kind of certainty to

where at least you could get, in those children whose clinicians have decided to use the drug, at least some basic pharmacokinetic data to find out that you are at least not overdosing them even if the indication is unclear?

DR. RIDDLE: Again, a very good question, and there hasn't been much dose response data generated recently, but there was quite a bit a number of years ago, and kids vary quite a bit as to what dose they may need, and where the field is, is start low, gradually move the dose up until you have kind of reached maximal efficacy and/or run into side effects that are problematic, and then back off a bit.

I think it is not that primitive because nobody has taken a look and tried to establish a good dose response curve. I think that the individual variability is so great that it's a wash.

Does that get at your question?

DR. NELSON: I guess it is unclear to me if it is the right time to just give up doing it, or if you just need more data to find out if it works.

DR. CHESNEY: Dr. Spielberg.

DR. SPIELBERG: In fact, Skip, I am not so much worried about overdosing as I am underdosing. I would bet that in a lot of the failed trials, given the more rapid clearance of almost every chemical substance on earth in

prepubertal kids, that, in fact, even though people were thinking they were increasing the dosing, I am not sure how much of that was really controlled by concentration and whether, in fact, many of these kids were chewing up drugs at heroic rates. I mean look at theophylline, when you carry kids at 40 mg/kg/day prepubertally, and they drop to 12 postpubertally.

I don't know how many of those studies really were concentration-controlled studies. Obviously, you are going to have to titrate individual kids, and from my understanding of depression or schizophrenia or anything else, it really is a titration and an empirical process.

But I am concerned that in some percentage of the trials that have been done, in fact, the kids really didn't have exposure despite increasing dosing.

DR. CHESNEY: Dr. Geller.

DR. GELLER: That is a really important point because the kinetics of kids, Dr. Vitiello did this first for lithium, is that they clear it more rapidly, however, just because of that, all of the studies that I know of have been concentration controlled, and usually what we headed for were higher concentrations in kids.

In my nortriptyline study of prepubertal depression, we were about a third higher than similar studies in adults based on what they would tolerate by

looking first at pharmacokinetic data. In our lithium study of prepubertal, we set our mark at 1.2, thinking that maybe if we did that, we could get response, but really as unbelievable as it is, although all these drugs do so really well in adults, it is very, vary hard to find an effect in kids when you are doing controlled studies.

That really has remained more than the safety issue and more than concentration issues. The problem has been finding things that give the kind of response we see when we are looking at an adult population.

DR. SPIELBERG: That is not surprising on a pharmacodynamic basis either from anesthetics and all the other literature in compounds that CNS in kids.

Were you at dose-limiting concentrations? In other words, if you go up to 1.3-fold what your mean concentration was in the adults, were you seeing things that were sufficiently distressing that you felt that that is as high as you could go?

DR. GELLER: With the tricyclic antidepressants, there were EKG issues, which was a cut-off, right. With lithium in prepubertal children, you start getting cognitive deficits, so that you have things that limit it aside from the concentration.

DR. WARD: Are the measurement tools effective for children, the ones that you would apply? In other words, do

you think there were changes, but you couldn't detect it with the measurement tools you were using?

DR. GELLER: This is really also another extremely excellent question. I honestly don't think that has been the issue. As Mark and Ben and Dr. Malone were saying, there has been a lot of effort put into developing instruments, and I don't think the issue has been that they are less developed than those in adults.

Of course, the age span, we don't have any biology. That is probably much more the issue than can we interview well enough.

DR. RIDDLE: Just a comment on the pharmacokinetics and the dosing. I can't comment on the field's past sins or whatever, but in terms of looking ahead, again, this preschool study, the design is to increase the dosing gradually and to have enough time to be able to get up to what we think are quite high doses or to stop if we have to before that, to be sure that we have given each youngster optimal dosing, and then we are going to be getting plasma levels.

We are not going to do individual PK curves, but we are going to get steady-state levels to look at that as part of the study.

DR. CHESNEY: Just refocusing on the first question, Dr. Laughren in his handout has three disorders

that you are considering requiring studies: schizophrenia, panic disorder, and conduct disorder.

I wonder if anybody in the room or any of our experts feel that that is something they should definitely look at or keep that under consideration? Yes.

DR. MALONE: One of the things I did want to say about the age group, I will say this and then I will go to the point of schizophrenia. The main concern is long-term safety, and I think that many of the studies that we get done, say, by industry don't really address that issue, so for that reason partly I wouldn't really be for making the studies be required in younger age groups, because we won't find out the key thing anyway, the long-term safety.

DR. LAUGHREN: But, of course, even if you look at kids, you know, 6 and older, or even if you limit it to adolescents, I mean you still have the same long-term safety questions that are very, very difficult to get at. I mean i's true of all drugs, it's true of adults, too. You worry more about kids because they have a longer life ahead of them.

DR. MALONE: And their brain is probably undergoing more development at a younger age, so they might be more at risk for the longer term issues.

DR. LAUGHREN: Right.

DR. MALONE: Although the brain is developing for

perhaps a fairly long period of time, perhaps in adolescence.

I could talk a little bit about the schizophrenia issue. If you are talking about preschoolers, you know, age 4 and under, schizophrenia is actually extremely rare. In fact, the studies that went to look at the difference between autism and schizophrenia looked at age of onset, and these studies were done in the seventies by Lauder in England, and if you looked at the age of onset and used an age of 5, if you develop symptoms before age 5, you have autism, otherwise, you are more likely to have schizophrenia.

DR. RIDDLE: A comment about these three disorders also. I think each of them is important and each has its own problems. The anxiety studies that have been done to date have not included panic disorder. We know that panic disorder occurs in adolescents. It is extremely rare in prepubertal kids.

I think studies in adolescents of panic disorder are called for. I don't think I would ask a company to do anything in the prepubertal kids.

Conduct disorder, you know, everyone knows is a very thorny issue, is it really a disorder, are we getting into behavioral control, is it really a list of kind of bad acts, if you will, and yet, there is a fair amount of pilot

small and controlled data suggesting that some of the psychiatric medications we use are actually quite helpful to youngsters with conduct disorder.

I think that we have to pay some attention to that, and it is a big problem.

You look like you are ready to respond.

DR. LAUGHREN: Well, I agree, I mean I think we could probably spend an entire day or more talking about conduct disorder because I share your concerns about the diagnostic criteria for that disorder. It is a list of mostly aggressive behaviors.

That was, in part, why I brought up the possible alternative route of looking directly at aggression rather than calling it something, you know, giving it another name that is not as nice as aggression, but that is really what is being treated.

DR. RIDDLE: My guess is that the experts in the field would say as long as there will be studies, go either way you want, just go, I think, because I think one could make an argument either way.

DR. CHESNEY: Is that the answer to No. 3 then, just go? They are asking there should we treat nonspecific symptoms or are nonspecific symptoms acceptable targets for drug development.

DR. MALONE: We study aggressive conduct disorder.

That is the main thing that I do right now is treatment studies for aggressive conduct disorder. Aggression is really a tricky thing. I think it would be hard to just study aggression alone because aggression is different in different diagnostic categories.

For instance, in children, I think aggression that occurs in conduct disorder and ADH would be different than, say, aggression that occurs in autism. I think there are very many issues about aggression that at this point in time at least, you still might want to restrict it to a few disorders.

For instance, in the adult studies, I think when they study, for instance, anger outbursts or aggression, they generally restricted it to personality disorders, and they would really rule out the presence of affecting disorder and psychosis and other disorders.

So, I think even though aggression does across many diagnoses, it probably is treated differently in the different diagnoses also. So, at this point in time, I think if you are studying aggression, you might really want to restrict it to a few disorders.

There is even the disorder, I think we had discussed this before, some impulse control disorder, in DSM that you could use partly, although I think it has problems also because I think you are required to have normal

behavior in between, and many of the aggressive individuals have other associated symptoms that go along with conduct disorder or ADH, in children at least.

DR. RIDDLE: In addition to aggression, I guess the other symptom that I think is fairly common and disabling, and is currently treated with major medicines, is "psychosis" or psychotic symptoms.

We know that schizophrenia is quite rare, and so if you have a new neuroleptic that has an indication for schizophrenia in adults, and then you want to go down in age, it is very hard to get much of a population, and even if you do, it doesn't generalize to many kids since schizophrenia in the younger population is fairly rare.

But psychotic symptoms in the prepubertal kids are I think fairly common and are treated with neuroleptics, and again with very little data. So, I would, particularly in the prepubertal kids, think about psychotic symptoms. Adolescent schizophrenia is okay, yes.

DR. LAUGHREN: So, you think it would be reasonable again in terms of invoking the Pediatric Rule, it would be reasonable to require companies to look at adolescent schizophrenia, that would not be an unreasonable thing--

DR. RIDDLE: Yes, I agree, I think that that is not unreasonable, but I worry also about the prescribing of

neuroleptics in the prepubertal kids with no data, and the only way we will get it is if you would ask for something, psychotic symptoms.

DR. LAUGHREN: But there again, the problem is how to define that. For schizophrenia, you have well-defined diagnostic criteria that you can apply in adolescents. If you get below that age and talk about psychosis, what is it that you are targeting, how do you define it, can you get agreement on that, all those sorts of things.

DR. CHESNEY: Dr. Geller.

DR. GELLER: I want to address that issue, but also add to what I think we need to ask companies to look at. When I talk to my colleagues around the country who also specialize in prepubertal bipolarity, the group at Harvard, and my own colleagues at Wash U., almost all the children we see with bipolar are on multiple medicines, and again without any data.

I think one of the things that if were possible would be to ask the companies to look at combinations, because we have almost no young bipolar children who get well on a single medication, and that is just widespread experience.

I have to temper that with how much of that is because we are doing it on an outpatient basis for kids that we most certainly would have hospitalized five years ago,

and does that change what you are giving. I think that is a question that has to be thought about.

In terms of the nonspecific diagnoses, I could not have more respect for Dr. Riddle and my other colleagues who think we should look at psychosis as an entity by itself or agitation or aggression as entities by themselves, so I am in the minority on this.

I think it is the wrong way to go because I think that it undermines the medical model which we have really fought so hard for in the last three decades in child psychiatry. Before 1970 or so, it wasn't even common clinically to interview children. You asked the mom what was wrong with them, and because of that, we didn't know depression existed because nobody was asking the child are you suicidal, and children, unlike adults, don't blurt this out when they walk into the doctor's office, you have to ask them, as I did to a child last week who was a consult.

Nobody knew she was suicidal, but when she was asked, the reason she has gone from an A to an F student is she is sitting in school all day thinking it would be nice to be in heaven. I still get chills. It's kids I have taken care of for years, and it is still startling to see a prepubertal child who wants to die that much.

My concern, if we start looking at broad categories is we are going to go back to that. The only

stethoscope we have as we have been talking about in child psychiatry and an adult is the interview.

I think we are at a point, certainly for bipolar and for depression, where we can interview very specifically and attach the psychosis to those diagnoses, and my concern, if we don't do that, is we will make a cottage industry out of studies of kids who have the broader categories, when, in fact, we have the ability to make better diagnoses and to begin attaching biology to them.

DR. VITIELLO: I don't know if I can comment?

DR. CHESNEY: Yes, please.

DR. VITIELLO: About the so-called nonspecific, I wonder if, in the same way that we can envision and conduct clinical trials of agitation and aggression in demented patients, in Alzheimer's, in the same way we can conceive clinical trials of an agent in children with mental retardation who are developmentally delayed and have brain damage, and who suffer from severe aggression and agitation.

It seems to me that that should be feasible and should be quite helpful. We have several suggestions that a large part of the use of antipsychotics in young children is for kids who are brain damaged in one way or the other.

DR. CHESNEY: Dr. Gorman.

DR. GORMAN: I would also like to be in the majority position for once this afternoon and support the

pursuit of symptomatic therapy. The treatment for ADD, as far as I can tell, is not curative, it is palliative. The children's disease does not go away. We just control its symptoms of hyperactivity/impulsivity, perhaps even aggression, and allow them to concentrate better.

So, you could argue that Ritalin is perhaps just a symptom controller of some of these symptoms. Aggression, I think is a major morbidity for the parents in children between the ages of 2 and 5, children who cannot attend preschool because they bite. Whether they bit because of impulse control or conduct disorder or autism, they all have the same morbidity in terms of their parents being unable to keep them in schools.

I think it is a very reasonable approach, and taking away a symptom does not always impair your ability to make a diagnosis. We try to take away coughs all the time, and yet we can still make the diagnosis of pneumonia very effectively and even asthma. Often, when we don't control those coughs with our symptomatic treatment, we know there is something more serious going on.

DR. CHESNEY: I think I understood Dr. Malone correctly to say that aggression could come from a variety of different causes, is that correct, from a conduct disorder, from autism, from ADHD?

DR. MALONE: Yes, and I wasn't speaking towards

whether we would use aggression as a thing to treat, that aggression itself is kind of a mixed-up symptom. If you are looking at different disorders, there might be a different drug that you would treat a different disorder with.

DR. CHESNEY: That was the message I heard, that if you used the same drug for all aggression, you might miss out on a better drug for the underlying problem.

Dr. Geller.

DR. GELLER: I wanted to go back to the examples that Dr. Vitiello gave. It is true that we treat the aggression in dementia, but we often have a particular diagnosis of dementia in mind. This is true of the multi-site dementia study that just started.

There is careful diagnosis using whatever biological markers are available, and then it is treating a symptom of illness much the way we would if somebody coughed, but had pneumonia. I think that is different than saying let's just take cough and not do everything we can to be sure that we haven't cultured and so forth to find out what the etiology is.

The other distinction I think I want to make is between what we do clinically and what we should be investigating. Clinically, we all treat what we see, because that's the best we can do in psychiatry, but I think research is obligated to go a step beyond that and see if we

can better define the entities that we are addressing the therapy to.

DR. LAUGHREN: I guess the question from our standpoint is what is the best model for going after these different symptoms or diagnoses, and I think what I am hearing from most of you is that although it might be reasonable to focus on a symptom like aggression, you don't view it in the same way that you might view a nonspecific symptom like pain or fever, that you would view it in the context of a particular diagnosis, and not a nonspecific symptom that has the same pathophysiology across diagnostic entities in the same sense that you might think of pain as having the same pathophysiology even though it is arising out of a lot of different diagnostic entities.

DR. RIDDLE: Yes, I think that is correct. I think we could have our cake and eat it, too, in terms of what we are talking about if one was really interested in targeting aggression. It could be aggression in kids with conduct disorder, or aggression in kids with a pervasive developmental disorder, or aggression in kids with mental retardation, or other examples.

I think one can always have a diagnosis to go along with the aggression, but the target of the drug may be the aggression within the diagnostic category.

Barbara, maybe that would satisfy or at least help

somewhat you and the medical model, and I think one could also do that perhaps with psychotic symptoms. There are quite a few diagnostic categories within the psychosis realm in the DSM, schizophrenia, schizophrenia form, psychotic disorder NOS, et cetera, et cetera.

So, I think that there are ways we could have a diagnosis and still not narrow the field too much and get at some of these symptoms.

DR. CHESNEY: Dr. Nelson.

DR. NELSON: But if you did that, are you thinking of a stratification where you would have to do your power analysis on the aggression, so that you have enough to answer within each strata, the question as to whether you have had an effect on the aggression, or do you want to lump that all together?

DR. MALONE: I would think you would be setting one diagnostic category at a time. So, for instance, if were studying young mentally retarded children who had severe aggression, and so they couldn't function, couldn't go to preschool, that you would really be looking at that symptom, perhaps other symptoms like hyperactivity, but you would be looking at one symptom and one diagnostic category. I mean maybe several symptoms, but aggression would be one of the key symptoms.

DR. CHESNEY: Dr. Gorman.

DR. GORMAN: Is it the consensus that aggression--and I am using that because we are talking about it--is a final common pathway of a biological cascade, or do you think aggression is unique is each situation as fever is, it is a final common pathway for many things? Is aggression unique in each disease, or is it the result of the cascade?

DR. MALONE: I would think it depends on the disease. For instance, in mania, some patients get very aggressive, and if you treat the mania, their aggression goes away, whereas, for instance, in conduct disorder, we are not really treating conduct disorder itself basically when we do our drug studies. We are treating aggressive behavior in conduct disorder, and we really target just the aggression.

So, it really depends on whether the disorder itself is causing the aggression, for instance, in some sort of psychotic disorder, like mania or schizophrenia, some of those patients have ideas or become very impulsive and get aggressive, and if you treat the main disorder, their symptoms go away.

Yet, there are other disorders like conduct disorder, it is true that most of the symptoms of conduct disorder are aggression, but when we are treating the aggression, I don't think we are really treating the core disorder, conduct disorder, we are really treating a

symptom. So, I think it really depends on the disorder.

DR. CHESNEY: Dr. Spielberg.

DR. SPIELBERG: The discussion sounds strangely reminiscent of some recent discussions we have had about cardiomyopathy. I mean basically, you can get a cardiomyopathy from thyroid disease, you can get it from amyloidosis, you can get it from hemosiderosis, or you can get it from viral infections.

So, if you treat the underlying condition, such as the thyroid disease, the cardiomyopathy goes away. Then, you are left with a large number of patients whom we still list as idiopathic, where you treat the symptoms of heart failure with ACE inhibitors and beta blockers and diuretics, or whatever else it is.

It sounds to me like we are saying with certain very specific conditions where aggression is associated with that disease, if you treat the disease, the aggression will get better. Manic depressive is a great example because we have very specific therapies for that, at least in adults.

But then we are left with a group of kids, you know, I used to follow a large number of kids with inborn errors of metabolism, who were retarded and developed aggression particularly around puberty, and the break point there was pharmacotherapy or institutionalization. These were truly life-threatening conditions where the aggression

regardless of the etiology was the primary driver for what would happen in that child and family's life.

In those circumstances where we don't understand etiology, just like we treat the symptoms of cardiac failure, is there a final commonality there, is there a way of grouping patients to be able to study that?

DR. MALONE: That is one of the things in our studies that we are trying to do, but there is only mainly lore about that. For instance, same conduct disorder. You can think of--well, actually, Dr. Vitiello has written about this--you can think of two major categories of aggression. One would be more impulsive/explosive aggressive behavior or affectively charged aggression, and the other type would be more planned aggression. You know, if you watch the Sopranos, you see a lot of planned aggression.

The idea would be that you could treat with medication the affectively charged type of aggression, but that if you give somebody who plans on doing things medication, they will still continue to do those things.

So, there are some gross subtypings, but they are not really that well worked out, and we don't have extremely good measures for determining whether you are in one category or another. Actually, in fact, probably many people with conduct disorder have both types. They plan some things, and some things are spur of the moment.

DR. SPIELBERG: I think what we are really all struggling over, I think we are all saying the same thing, we are concerned about these kids, we are concerned about their families, we are concerned about the societal consequences. If you had to pick a serious and life-threatening illness, this outdoes childhood cancer considerably in terms of numbers.

The issue, though, is how do we study it. At the October meeting, I think we are going to have to come to grips with what kind of study designs are reasonable, what kind of drugs are reasonable, and then get on with the business of trying to study the kids, and actually get some data.

DR. MALONE: Amazingly enough, I think it is quite an understudied area, and I think there are so many things that go into, for instance, having a conduct disordered child be aggressive that it is hard to know all of them, you know, the environment, the family situations, and biology. So, there are all these things going on at the same time, and, you know, for instance, I think, it is just my impression, you know, we have done inpatient studies where the setting is very controlled, and now we are doing outpatient studies.

In our studies, you go through a placebo period, and if you are not showing the aggression during the

baseline washout period, you don't get into our study. I think that was much easier in the inpatient study where we would then end up with one certain subtype of patient to show that a medication will work than it would in an outpatient setting.

I don't know that medications are the total answer for aggression. I think there is a lot of psychosocial and other work that needs to go on before we can learn how to treat aggression.

DR. CHESNEY: Dr. Laughren and Dr. Murphy, has this group of people given enough input in terms of the three questions, or are there still issues you would like to have to discuss?

DR. LAUGHREN: Let me take a stab at summarizing what I have heard, and see if there is any consensus on this.

Basically, in terms of the three entities that we have targeted under written requests - major depressive disorder, OCD, and GAD, what I am hearing is that the age cut-offs that we have been using are reasonable, that there is no compelling reason to go below age 6-7 in terms of those diagnostic entities.

For schizophrenia and for panic disorder, it probably makes sense to look into adolescents, but no below at this point. Then, my sense is that for almost everything

else, it is still perhaps too murky for us to be taking any definitive actions under either the written requests or the Pediatric Rule. In terms of even looking at ADHED under 6, we might best wait until we see more of the results from the PATS study before we proceed in that area.

Conduct disorder is an interesting, obviously important problem, but not so clear that there is any compelling reason for us under our existing tools to be forging ahead.

There doesn't seem to be a consensus at this point that the nonspecific symptom approach makes a lot of sense at this point at least in terms of again these tools that we have before us. It doesn't make sense for FDA to be taking the lead in encouraging studies when there is so much I think uncertainty about what is the right way to go.

In terms of autism, again, obviously, there is a lot of work that needs to be done. It is not so clear that it is ready again for FDA to be encouraging drug development with the current drugs that we have.

Dr. Vitiello pointed out that there is no clear rationale for going forward with those kinds of programs with the drugs that we have, at least in terms of FDA taking the lead in encouraging that.

DR. CHESNEY: Dr. Kauffman.

DR. KAUFFMAN: I just wanted to ask Dr. Laughren,

having said what you just said, and given that you would not take the lead in a couple of these diagnoses, for example, autism or conduct disorder, would that have an impact on what you would necessarily do if a sponsor took the initiative on one of these indications that at this point in time we don't feel that the FDA should take an initiative on? In other words, if a company came to you with a new chemical entity that they said we would like to try this in autism, would you listen to them, or would you say we don't think that is something we really want to focus on right now?

DR. LAUGHREN: I agree, that is an entirely different question. Of course, we would listen, but we would caution them that it is a new area, and we don't have any precedence, and we would have to rely on the advice of outside experts. Of course, we would listen and would be interested in what they proposed.

DR. MURPHY: I think the quandary here, as you are well aware, is that is why we bring some of these issues forward for public discussion, is that they may also ask us to issue a written request, so that they may gain the six months of exclusivity, because they think there is a need.

DR. KATZ: We did that with the sleeper, with the insomnia.

DR. MURPHY: Right. So, that is clearly one of

the goals we wanted to hear the discussion, because as Tom has laid out, this is what we are doing right now, this is what we have heard from you, that we think we should do in the meantime while we continue to get inquiries into various areas of a possible study.

DR. CHESNEY: Dr. Riddle, the last word.

DR. RIDDLE: I think your summary was very accurate. I think the only additional comment is that it concerns me with the new neuroleptics that are coming onto the market, and the concern we have about the impact of chronic neuroleptics in kids, that given what you said, I think the only studies that would then be done would be with adolescents with schizophrenia, and yet there is so much prescribing going on for conduct disorder or aggression and other "psychotic" symptoms, that it leaves me wishing that you could push that envelope a bit whether it is conduct disorder or something besides adolescent schizophrenia.

DR. LAUGHREN: I am going to encourage Ben under his authority at the NIMH to promote those kinds of studies to look at safety.

DR. VITIELLO: We will try.

DR. MURPHY: I think that is why we are participating in this research meeting, is that we would hope that we can hear some more discussion about how this field can be moved forward.

DR. CHESNEY: As you all know, Memphis is the Northwest hub, and Northwest prides itself on an on-time departure, and as a "Memphian," I note that it is 5:25.

I wanted to thank Dr. Laughren, Dr. Malone, Dr. Riddle, and Dr. Vitiello very, very much for educating us all and for responding to the questions on our behalf.

Tomorrow's meeting starts at 8 o'clock.

Thank you.

[Whereupon, at 5:25 p.m., the proceedings were recessed, to resume at 8:00 a.m., Tuesday, September 12, 2000.]