ajh

ATDEPARTMENT OF HEALTH AND HUMAN SERVICES

FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

PEDIATRIC ADVISORY SUBCOMMITTEE

A SUBCOMMITTEE OF

THE ANTI-INFECTIVE DRUGS ADVISORY COMMITTEE

ETHICAL ISSUES

DAY I

Monday, November 15, 1999

8:00 a.m.

MILLER REPORTING COMPANY, INC.
507 C Street, N.E.
Washington, D.C. 20002
(202) 546-6666

Holiday Inn Silver Spring
Kennedy Grand Ballroom
8777 Georgia Avenue
Silver Spring, Maryland

PARTICIPANTS

P. Joan Chesney, M.D., Chairperson
Jayne E. Peterson, R.Ph., J.D., Executive Secretary

MEMBERS

Judith O'Fallon, Ph.D.
Keith Rodvold, Pharm.D.

VOTING SGE CONSULTANTS

David Danford, M.D.
Kathryn Edwards, M.D.
Robert Fink, M.D.
Mark Hudak, M.D.
Richard Gorman, M.D., FAAP
Naomi Luban, M.D.
Robert Nelson, M.D., Ph.D.
Victor Santana, M.D.
Stanley Szefler, M.D.

NON-VOTING CONSULTANTS

Ralph Kauffman, M.D. (AAP)
Stephen Spielberg, M.D., Ph.D. (PhRMA)

GUESTS AND GUEST SPEAKERS

Jeffrey R. Botkin, M.D., M.P.H.
Ellen Clayton, M.D., J.D.
Norman Fost, M.D., M.P.H.
Eric Kodish, M.D.
Susan Kornetsky, M.P.H.
Jonathan Rackoff
Leroy Walters, Ph.D.
Robert Ward, M.D., FAAP, FCP
Benjamin Wilfond, M.D.

FDA

Dianne Murphy, M.D.

C O N T E N T S

Page

Call to Order:
P. Joan Chesney, M.D. 5

Conflict of Interest Statement:
Jayne E. Peterson, R.Ph., J.D. 5

Welcome and Review of Meeting Agenda:
P. Joan Chesney, M.D. 6

Background and Information and Overview:
Dianne Murphy, M.D. 8

Compliance Issues:
Paul W. Goebel, Jr. 22

Institutional Review Board Issues:
Susan Kornetsky, M.P.H. 33

Pharmaceutical Research and Manufacturer's Association:
Stephen Spielberg, M.D., Ph.D. 47

Investigator Comments:
Ralph Kauffman, M.D. 61

Questions and Comments from the Advisory Subcommittee 75

Presentation of Case Studies/Questions:
Dianne Murphy, M.D. 80

Topic Presentations

Research on Healthy Children: History
Jeffrey Botkin, M.D., M.P.H. 86

Benefit in Pediatric Research:
Norman Fost, M.D., M.P.H. 101

Risk in Pediatric Research:
Benjamin Wilfond, M.D. 122

Assent/Consent/Permission:
Ellen Clayton, M.D., J.D. 138

Compensation:

Jonathan Rackoff 153

Subject Selection, Ethics and Pediatric Research:
Eric Kodish, M.D. 168

C O N T E N T S (Continued)

	PAGE
Open Public Hearing	
Dr. John Wilson	181
Dr. Susan Weiner	186
Comments of Dr. Alan Zametkin (read by Dr. Chesney)	188
Committee Discussion	
Case Study No. 1	189
Case Study No. 2	210
Case Study No. 3	241
Case Study No. 4	257
Case Study No. 5	281

P R O C E E D I N G S

Call to Order

DR. CHESNEY: Welcome to the first day of the Pediatric Advisory Subcommittee. The microphones on the table are not working yet so we are going to leave the introductions until the question and answer session. But I would like to have the Executive Secretary, Jayne Peterson, 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. Since the Subcommittee's discussions will not have a unique impact on any particular firm or product but, rather, may have widespread implications with respect to an entire class of products, in accordance with 18 USC, Section 208, general matters waivers have been granted to each member and consultant participating in the subcommittee's discussions.

A copy of these waiver statements may be obtained by submitting a written request to the FDA's

Freedom of Information Office, Room 12A30, of the Parklawn Building. In the event that the discussions involve any products or firms 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 involvement with any firm whose products they may wish to comment upon.

Welcome

DR. CHESNEY: As everybody in this room knows, on November 21, 1997, President Clinton signed into law the Food and Drug Administration Modernization Act which provided, as I quote from one of the FDA statements, "the most sweeping changes to the Federal Food, Drug and Cosmetic Act in thirty-five years."

One of these changes was to offer six months of additional marketing exclusivity for companies providing pediatric studies in response to a written request by the FDA. The FDA Final Rule of 1998 required companies to

provide pediatric studies for certain new and marketed drugs and biological products unless a waiver was obtained from the FDA.

Today, we will be reviewing one of the most fundamental issues involved in pediatric studies. I quote from one of the handouts in our books, "the criteria for the appropriate involvement and exclusion of healthy children who are not patients in pediatric pharmaceutical research."

This issue involves questions of risk/benefit, consent and assent, particularly for children under seven years of age who are considered to be unable to grasp the issues involved in consent, and questions of compensation for both the child and the parent.

We are very fortunate today to have a number of distinguished speakers to provide us with the background information needed to address the five case studies the FDA has provided to the subcommittee. It is hoped that today's discussion will provide the infrastructure for all future deliberations regarding the participation of healthy children in pediatric studies.

On behalf of the subcommittee and the FDA, I

would like to welcome all the consultants and guests and members of the audience. Particularly, I would like to welcome two members of the International Committee on Harmonization, Dr. Julia Dunn, who is from the United Kingdom. She is the member of the Medicines Control Agency there. And Dr. Siddika Mithani, who is head of the Cardiovascular Diseases Unit at the Bureau of Pharmaceutical Assessment in Canada.

Finally, just a few housekeeping issues. First of all, the Open Public Hearing will take place at 1:30 this afternoon and not 11:30 as advertised in the Federal Register. Because we do have a number of speakers and a busy program, we will be using a timer. We would ask the speakers to keep to their allotted times.

It will be particularly challenging to stay on track today, as it always is with ethical issues, and we would very much appreciate everybody keeping the word "brevity" in mind. Finally, if I don't identify you by name, please do so when you answer a question or make a comment in order to help our transcriptionist.

And so we eagerly look forward to hearing all the information we are going to be presented with this

morning. I would like, at this point, to turn it over to Dr. Dianne Murphy.

Background

DR. MURPHY: Good morning.

[Slide.]

Again, I would like to second the welcome to our members and to our guests and consultants to what will be the first in a series of discussions as far as the FDA is concerned.

This is only the beginning of the discussion and we hope to see not only an excellent review of this matter today but advice which we can then turn into a form of action for our internal use because the one point I did want to make particularly today is that this is not a hypothetical or theoretical discussion.

The FDA is dealing with these issues every day and the cases that you will have before you, or have before you, are real situations with which we are dealing.

I am going to provide a little bit of background on how the day will proceed and then some background as to how we got to this position, if you will, today or

where we are.

[Slide.]

You will see from the agenda that we will be talking about the limits of FDA's oversight, if you will, the role of IRBs, the perspective of industry, the perspective of physicians who are actively enrolled in clinical trials, and that is the background part that will happen early this morning.

Then, we will be looking at the questions. We will not be discussing the questions, but we want everyone to have them in mind, so we need to present them publicly, so that everyone will have a context in which to think about the presentations by our speakers and consultants and guests.

Then, we will have a presentation by our experts in the field of ethics, and then we will ask the committee to go through the cases and answer the questions that we have presented to them.

[Slide.]

This is a slide that this committee has seen a number of times, but I felt it important to review as we go forward today. You will note that there are three

major events that have occurred after decades literally of effort to provide a mechanism, an approach to enroll children in clinical trials.

The American Academy of Pediatrics, many professional societies in the FDA have been dealing with this issue on record as policy since the seventies. In 1994, the Food and Drug Administration passed a regulation which dealt with a very important concept that we had hoped would bring the seal forward, and that is, the idea of extrapolation of adult efficacy where appropriate.

I am not going to go through those definitions because this committee had a whole session on that last time about when one can extrapolate or not extrapolate from adult data, but it is clear that, two things - one, we can't always do that; and, two, that the response to that activity or that regulation was not what the FDA had hoped and, in essence, we continued, if you will, in the same manner of a situation which existed where still two-thirds to 80 percent of products being used in children were not labeled for use in children, and we were, in essence, experimenting every day on children.

So, in 1997, as Joan has noted, Congress took things into its hands and passed the Food and Drug Modernization Act. In that Act, there was a section 111 on the availability of extension of marketing exclusivity if you conduct pediatric clinical trials.

Now, this is really the engine driving the machine, if you will, right now, and I will speak a little bit more about that.

In addition, the FDA passed regulations in December of 1998, which we call the Pediatric Study Requirements. These are frequently referred to, of course not by the FDA, but others, as the carrot and the stick.

I feel that the sum is greater than the parts, because we think one of the reasons that this is so successful, the Food and Drug Modernization Act offering of exclusivity, is that if you don't do it when you can obtain a benefit, and you come back in later, you will have to do it anyway.

[Slide.]

This is a slide for which you should take no numbers down, because they are basically inaccurate, and

you are going to say, well, why am I showing this - because I am continuously asked where are we as far as the pediatric rule is concerned, and one of the things I wanted to point out is that as of April 1999, if you have an application in the FDA, you were supposed to have in it if this product is going to be used in children--well, whether it is going to be used in children or not, you need a waiver if it is not going to be used in children--but you need to have in that application either a waiver if it is not going to be used in children, a deferral, or the pediatric study.

People are saying, well, how many studies have resulted because of the rule. I think it is very important to people to realize that the rule, under the rule, even though it went into effect and applications need to have one of those three things in them as of April, we cannot require studies until the end of next year, so that when I tell you that these are not--this doesn't include supplements, but that there are approximately 45 NDAs that have been approved since April, you will see that these numbers don't add up, and one of the reasons that they don't add up is that many of

these studies or some of these studies were asked for previously and the Divisions are now processing them, if you will, the way they always have, but now they have an additional piece of information they are having to enter because we have a new tracking system.

So, the other thing that we are pointing out here is that QA-ing our tracking system, as you will see, that the numbers don't add up. We are still trying find out what has happened with the rest of these because if you say we have 45 approvals, 6 of those had waivers in them--and I will put the next slide up, that will show you what those waivers were--there were 13 approvals with studies completed meaning they had pediatric studies in them, and if you realize that this is actually an increase in what we would have expected, so we can see that there is some activity that is already being seen, and that we have deferred only 7, and this is the area that is new and everybody is trying to learn how to document that because these may have been Phase IV studies and we do track those, and they are just not entering them as deferrals.

So, right now this is where we are on the

Pediatric Rule in that we are beginning to look at this process as far as waivers and deferrals, but I don't think--and the reason I want the committee to be aware why we weren't giving them more information at this time--that we didn't have all of the tracking system QA done that we would like to have, but it does give you an idea of what is going on in the way of application submissions with pediatric studies being completed.

[Slide.]

Of those applications that had waivers in them, these were the indications which had waivers, and I think most people would agree. I want to point out something. This says "partial or complete waivers," and that means that it could be a complete waiver as you would expect for testicular cancer in that it does not occur in the majority of the pediatric population, or it could be a partial waiver where you waived all of the pediatric population except a certain age group.

[Slide.]

So, what is happening that is really, as I said, the engine driving the activity in pediatric clinical trials is FDAMA, and we say that because even though

FDAMA was passed in November of '97, the implementing guidances, if you will, do not occur until the summer of '98, and so we now have, since that time, have received already 159 proposals from industry.

This is a dramatic change to study children, and from those proposals, FDA, what the legislation required, as the committee is aware, is that FDA make an assessment of what studies need to be done to provide a substantial health benefit, so this has been a tremendous burden for FDA, one which we were glad to get, but we are trying to decide which studies need to be conducted.

We have issued 101 written requests to sponsors asking them to study children, again fairly dramatic. If you remember some of the prior information we presented about over six years having only 71 studies.

[Slide.]

What type of studies are we asking for? I put this up for two reasons, because I wanted to point out that of the 101 written requests that we issued, we asked for 228 studies, which means every written request has at least two studies in it, and that these studies, many of them were still efficacy studies.

We felt we did not have enough information for a variety of reasons that we won't go into today, that we needed to ask for an efficacy study.

[Slide.]

Of these 228 studies, we know from 102 of them how many children were requested to be enrolled in the studies. Now, you can say why didn't you know for all of them, because some of them were statements like adequate numbers to achieve a difference of or power to, so they don't have exact numbers.

Where we do have exact numbers, the point is only 102 of these studies out of 228, almost 15,000 children that would be involved.

[Slide.]

Children are being enrolled in clinical trials, and that is why we are here.

[Slide.]

We know--and these conclusions are my conclusions, I tried to summarize some of the things that I think brought us to the point that we are today--that there are differences in the physiology and development that are important and that we need to look at them in

children, where you cannot look at them in adults.

[Slide.]

And ignorance is our greatest risk, and as has been clearly stated over the last two decades, that in essence we cannot continue this decades long daily experimentation without gathering knowledge and information as to what we are doing. We need to study, have children involved in clinical trials. That is this summary, or we will end up--this is sulfanilamide bottles that everyone now knows--where children had the right to have a new antibiotic just as well as adults, but instead of studying how to get that product available to children, it was simply dissolved in a solution, which then caused renal failure and death, so this is one of the great examples of why things which may appear fine on the face of them, may not do well in children, didn't do well in adults either.

[Slide.]

Our knowledge gap is large, and I think this is one of the things that we have really been struggling with, is that because we haven't been doing studies in children, and many of the products that we are using in

children, we don't have some of the science foundation that we would wish to have.

By that, we are learning much about the differences in physiology and maturation of enzymes and CNS, but endpoints, you may have a wonderful endpoint to study depression in adults, but you may not have such a validated, well-studied endpoint in kids, or if you do, how far down can you go with that or how far down should you go with that.

So, there are tremendous knowledge gaps that we are having to deal with as we move forward in this process.

[Slide.]

And that certain processes require children in them. The thin skin of the neonate and the premature cannot be duplicated with adult skin, and only a child can tell you whether it tastes good, that they will take this medicine.

[Slide.]

Legally, children cannot consent, and in your handout you had some very nice articles that discussed this issue, and that everybody, the Commission, the

Academy, and many of our guidance have indicated that we have a very high bar to pass if we are going to enroll children in clinical trials.

It is our collective responsibility to ensure the well being of children who participate in these clinical trials.

[Slide.]

To be politically correct, there should be a gentleman in here also as we go forward into this era, carefully guiding our children in clinical trials.

[Slide.]

As we do it, we need to recognize some other issues. The reason that this arena has changed is economic issues, and companies are going to receive an economic incentive, and it was felt correct that they should.

That is not the issue. It is just we have to recognize that that is part of what is important here and driving it, to develop pediatric clinical trials, that some families may need the money, and there may be--and this I am quoting from some investigators and other people who are now involved in clinical trials--is that

there actually be a "shortage" of children, of certain ages, or with certain diseases, to participate in studies.

I have no facts to present you on that. It doesn't say conclusion, these are just things that we are hearing, if you will, at this point.

[Slide.]

So, we are here today to look at what the FDA does all the time. We know when we approve a product for use by the American population, there will always be a risk. So, are used to doing this, and we understand there has to be some risk involved. There will always be somebody will not tolerate a product.

But how do you balance this, how do you make it as safe as possible? What are the benefits, what are the risks for children to participate in trials? The question today is: What if there is no direct benefit for child?

[Slide.]

As we go forth in this discussion today, there is a book called, "The Third Chimpanzee," by Jared Diamond, and he has a chapter called, "Nothing Learned

and Everything Forgotten." I think that is very important. Again, as you saw in your handouts, it was a very, very good review of much of what has happened in the field in which children have been the vulnerable population throughout history and have been used rather indiscriminately as trial subjects.

It seems like in reading the articles, one of the highest risks is to be a child of a physician, but at any rate, we need to learn from what has happened in the past.

[Slide.]

As Arthur Wichmann was quoted, a Dutch explorer who spent his life writing about what happened to New Guinea, is that they, "committed the same stupidities again and again; unwarranted pride in overstated accomplishments, refusal to acknowledge disastrous oversights, ignoring experience of previous explorers, consequent repetition of previous errors, hence a long history of unnecessary sufferings and deaths." We, of course, want to avoid this.

[Slide.]

"Among the hopeful signs, there are many

realistic, often-discussed policies by which we could avoid disaster..." Again, from your handouts that our experts have provided, you can see that this is an ongoing discussion, and we at FDA are participating in this now in a very public forum.

[Slide.]

There will be a public discussion of the ethical issues surrounding the participation of children who will derive no direct benefit in clinical trials. That is our statement. We can decide whether that really is the question.

[Slide.]

We hope to discuss that if there are situations-- and you will see, and so we don't have to repeat the phrase "pediatric population who will derive no direct benefit," we have tried to synthesize that down to either "normal pediatric volunteers" or "healthy children," you will see those different phrases interchangeably--who could participate in pediatric clinical trials, and if so, if the answer here is yes, are there parameters we can use to define these situations.

This is in face of what we know is out there already in the way of recommendations from the Commission and also the Health and Human Services Subpart D, which you will hear about this morning.

[Slide.]

The presentations that you see today will be posted on our web site, so that those of you who wish to refer back, because we have so much expertise with us this morning, we thought it would be very helpful to have this material available, and we will do so. Give us a week or two after the meeting to get it up.

At this point, I have done my background part and I would like to introduce now Paul Goebel, who is our Associate Director for Human Subject Protection at CDER, and he will review the regulations and the guidances that are in place.

After he speaks, Susan Kornetsky, who has been with the IRB at Children's Hospital in Boston for I think over 17 years--is that correct, Susan--yes, will be speaking.

Steve Spielberg, who is going to present the perspective of the industry that is participating and

conducting many of these trials, and Steve has a very illustrious background in both research and in drug development, and has also been the chair of the International Conference on Harmonization document on development of clinical trials in pediatrics, because many of these studies are being done globally, which I think is another important point for people to think about as we go through the day.

Dr. Kauffman from Children's Mercy Hospital in Kansas City, who is very active in the pediatric pharmaceutical research unit, and also brings to us a perspective as somebody who is doing these trials on a regular basis, and how he sees this issue.

At that point, we will have the questions and comments from the Advisory Committee for clarification of the morning speakers, and then I am going to come back after the break and introduce the guests and the cases.

Thank you very much.

Compliance Issues

MR. GOEBEL: Thank you, Dr. Murphy.

[Slide.]

This discussion will outline the regulatory

requirements and guidance that apply to protection of pediatric study subjects.

The following slides will illustrate the regulatory and legal status of regulations and guidance documents.

[Slide.]

Regulations have the force of law. FDA may refuse to accept studies that are not in compliance with FDA regulations. IRBs, clinical investigators, and sponsors may be the objects of FDA enforcement actions for failure to meet the requirements of the regulations.

[Slide.]

Guidance documents, on the other hand, reflect current FDA thinking, an acceptable approach to meeting the requirements of the regulations. Guidance is not binding on FDA or the regulated industry.

Alternative approaches are acceptable if the requirements of the regulations are met.

IRBs, clinical investigators, and sponsors generally follow FDA guidance with respect to protection of human subjects of research. FDA will not initiate an enforcement action solely on the failure to follow the

process outlined in a guidance document, however, failure to meet guidance would also mean failure to meet the regulation unless an acceptable alternative process is in place.

[Slide.]

The FDA regulations for human subject protection consist of the Part 50 requirements for informed consent and the Part 56 requirements outlining organization and function of an IRB and the records that an IRB must keep.

FDA gains its jurisdiction through the product. These regulations apply to studies in human subjects of FDA regulated products, most commonly drugs, biologics, and medical devices.

[Slide.]

It may be helpful to point out two items that the FDA regulations do not contain. There is no mention of assent by children. There are no regulations outlining the specific additional protections that should be in place when conducting research in pediatric subjects. The only mention of children is their inclusion as examples of vulnerable categories of subjects.

[Slide.]

The FDA informed consent regulations contain general requirements, as well as specific elements that must be included in informed consent. This discussion will not cover the entire set of regulations. The following two slides show portions of the informed consent regulations that are of special interest for protection of pediatric study subjects.

[Slide.]

This slide illustrates that FDA requires understanding of the consent information by either the subject or the subject's legally authorized representative, but not both, also minimizing the possibility of coercion or undue influence applies to either the representative or the subject, but not both. There is no requirement for understanding or assent by pediatric study subjects.

[Slide.]

The regulations do not explicitly mention payment for participation in studies, however, FDA regards payment as a benefit, but not a medical benefit, that should be approved by the IRB and outlined in the

informed consent document.

[Slide.]

Turning now to IRB membership, this section encourages, but does not require that individuals knowledgeable about and experienced in working with children be included as members of IRBs reviewing pediatric studies.

[Slide.]

However, there is a requirement that IRB members have sufficient expertise and experience to completely and adequately review the study, including determining that it meets standards, professional conduct, and practice.

This requirement may be met by either of two means: either the qualifications of the established membership of the IRB or by the use of consultants.

[Slide.]

The regulations list eight criteria that the IRB must determine are satisfied before the IRB approves a study. Two of the criteria mention vulnerable categories of subjects.

[Slide.]

The IRB must assure that the selection of subjects for pediatric studies is equitable. For example, appropriate safeguards must be in place when institutionalized children are to be enrolled. No specific requirements are outlined, but the IRB is clearly required to know the population from which pediatric studies are being selected.

[Slide.]

This section requires additional safeguards to be in place when vulnerable subjects are included in the study. Again, it does not specify or otherwise outline what those safeguards should be, but the IRB is required to know when study subjects are from vulnerable populations and to require safeguards to protect their rights and welfare.

[Slide.]

Studies conducted outside the United States and not under an IND may be submitted to FDA. These studies are not required to meet FDA's IRB and informed consent requirements, but must meet either the Declaration of Helsinki or the laws of the country in which the study is conducted, whichever provides greater subject protection.

[Slide.]

The Declaration of Helsinki requires a minor child to give consent when the child is capable of understanding the concept.

[Slide.]

Turning now to guidance published by FDA, the ICH agreement will be specifically discussed.

[Slide.]

The International Conference on Harmonization is a body composed of representatives of the regulators and the drug industry of three areas of the world - the United States, the European Union, and Japan. The FDA has published the E6 Good Clinical Practice Agreement as guidance, not as a regulation.

[Slide.]

The ICH requires children to be informed, to give assent, and to sign the consent form to the extent they are capable of understanding.

[Slide.]

The ICH states that trials with no anticipated clinical benefit should be conducted only in those who personally consent, sign, and date the consent form.

[Slide.]

However, these is an exception to this rule. Surrogate consent is acceptable when all of the following conditions are met: the trial objectives can't be met by including only subjects who personally consent, the foreseeable risks to the subjects are low, the negative impact on the subject's well-being is minimized and low, the trial is not prohibited by law, the IRB or IEC agrees to inclusion of such subjects, and the informed consent covers this aspect of subject selection.

[Slide.]

The ICH required two additional safeguards for such trials. They should be conducted in patients with the disease under study unless an exception is justified.

Study subjects who cannot consent and who are not anticipated to personally benefit should be closely monitored and withdrawn if they appear to be unduly distressed.

[Slide.]

In addition to the FDA regulations, there are two other sets of federal human subject protection regulations that pertain to some pediatric clinical

studies. These are the so-called Common Rule and the Department of Health and Human Services regulations.

[Slide.]

The Common Rule is administered by each of 17 federal agencies for studies funded or conducted by that agency. FDA-regulated studies are not included.

[Slide.]

The HHS regulations are administered by the Office for Protection from Research Risks, which is presently located at NIH.

The HHS regulations apply to studies funded or conducted by employees of any HHS agency including FDA. They also apply to all studies conducted at sites with a Multiple Project Assurance from OPRR, such as most children's hospitals.

FDA does not enforce the HHS regulations and they do not apply to FDA-regulated studies, such as those funded by commercial sponsors.

[Slide.]

There is an overlap where both FDA and HHS regulations apply. You see the FDA regulations are here, conducted by commercial sponsors. The HHS regulations

apply here for studies funded by federal agencies, but in the middle, we have children's hospitals and other institutions with a Multiple Project Assurance from OPRR, and in that case, both sets of regulations apply and must be complied with.

[Slide.]

There are four subparts to the HHS regulations. Subpart A, the basic portion, is identical to the Common Rule, and is essentially identical to the FDA rules.

The HHS regulations add three subparts that are required when studies are conducted in a special population. Subpart B is fetuses, pregnant women, and in vitro fertilization.

Subpart C is prisoners, and Subpart D is when children are subjects of the research.

[Slide.]

Subpart D contains specific additional protections for pediatric studies funded by HHS or conducted in MPA institutions. Again, both the FDA and Subpart D regulations apply when FDA regulations are conducted at sites with Multiple Project Assurances, such as children's hospitals.

[Slide.]

The additional safeguards imposed by the HHS regulations vary according to the risks and benefits to the children. For minimal risk studies, permission of one parent and assent of the child is required. Permission in HHS speak is equivalent to the FDA term informed consent by a legally authorized representative.

[Slide.]

If the study imparts more than minimal risk and presents the prospect of direct benefit to the individual child, three conditions must be met: the risk is justified by the anticipated benefit to the children, not just the overall benefit of conducting the study, the risk-to-benefit ratio should be at least as favorable as the available alternative approaches, and assent of the child and permission of one parent should be obtained.

[Slide.]

If the study imparts more than minimal risk or presents no prospect of direct benefit to the individual child, and there is only a minor increase over minimal risk, the following conditions must be met: the process should be similar to actual or expected medical

situations the child would encounter outside the study, the study is likely to yield vitally important knowledge to the child's disorder or condition, and assent of the child and permission of both parents is required.

[Slide.]

If the study does not qualify for the previous sections, then, lots of bureaucracy is involved before the study can proceed.

[Slide.]

The first test is that the research presents a reasonable opportunity to further progress in solving a serious problem affecting the health or welfare of children, several things have to happen: the study must be reviewed by an expert panel, there must be public review and comment, and the Secretary of the Department of Health and Human Services must find that the study either meets one of the less stringent standards or the research again presents a reasonable opportunity to further the understanding of a serious problem affecting the health or welfare of children, the study is based on sound ethical principles, and assent of the child and permission of both parents is required.

This process is not easy to accomplish and has seldom been attempted.

[Slide.]

The HHS regulations also outline the conditions under which assent and parental permission is required. The IRB determines whether children are capable of assent. This decision can be made per protocol or per child. If the research holds out the prospect of being direct benefit to the children, assent is not required.

[Slide.]

Permission of parents is required except parental permission may not be reasonable in case of neglected or abused children.

Permission of parents should generally be documented, most commonly by their signatures on the informed consent form.

The IRB decides whether assent of the child needs to be documented and the extent to which it must be documented.

One other guidance document will be discussed.

[Slide.]

The American Academy of Pediatrics has published

detailed guidelines outlining the ethical conduct of studies in children. It is included as a reference only, although helpful and often referred to, the guidelines are not included in FDA or other official federal regulations or guidance.

This has been an overview of the federal requirements for protection of the rights and welfare of pediatric subjects of biomedical research.

Thank you.

DR. CHESNEY: Thank you very much.

Our next speaker is Susan Kornetsky from Children's Hospital in Boston, and she will be speaking about Institutional Review Board issues.

Institutional Review Board Issues

MS. KORNETSKY: Good morning.

[Slide.]

I am honored to be able to provide the Pediatric Subcommittee with some IRB perspectives about pediatric research.

[Slide.]

Although the pediatric regulations have been in effect since 1983, new NIH and FDA initiatives further

challenge the ethical approaches we use to comply with the regulations.

Through this presentation, it will become clear that currently, IRBs are challenged in how to interpret and ethically apply the pediatric regulations. New initiatives, such as enrolling normal children or children without a specific disease will be of tremendous concern if they are even possible to approve.

[Slide.]

My presentation is divided into five sections. I have been asked to provide a brief overview of the regulations. Paul has done a very nice job of that, so I am going to go through that very quickly.

This overview is critical and will put into context the issues we will consider today. In preparing for this presentation, I also have spent time gathering ideas from other members of the IRB community, and I will present a synopsis of the questions and answers I received.

Finally, I will end by reviewing what I believe will be the major IRB concerns if and when protocols involving normal children and those without the disease

are reviewed by an IRB.

[Slide.]

FDA does not specific regulations for the use of children in medical research. Health and Human Services contains Subpart D. As an IRB with an MPA, they must apply the special protections to federally-funded research. Many IRBs also choose to apply the special protections for children to all pediatric research regardless of funding source. Therefore, Subpart D in some situations is applied to FDA-regulated studies.

I need to also add that OPRR is presently very concerned that Subpart D is not being adequately applied. This has been a common concern on their site visits.

In contrast to the general human subject regulations applied to adults, the special protections for children specify a risk-benefit threshold which serves as a stop sign. When you reach this threshold, you need to stop and consider some very critical issues and then proceed only if conditions are justified.

The good clinical practices of the International Code of Harmonization do not include a separate section for children, however, they do specifically recognize

non-therapeutic trials in subjects with legally acceptable representation.

[Slide.]

The regulations divide pediatric research into four categories. Paul went over them. A Category I is involving minimal risk with and without benefit, Category II is greater than minimal risk with direct benefit, Category III and Category IV, greater than minimal risk with no prospect of direct benefit. Category III is the stop sign I was referring to, and you can proceed if specific conditions are met. Category IV requires and HHS panel for all federally-funded research. According to OPRR as of last week, this option has only been used twice.

[Slide.]

These are just the different categories that Paul went through, so I am going to quickly go through them. Category I, there really are no overriding ethical concerns. Category II is research presenting greater than minimal risk with a prospect of direct benefit.

[Slide.]

Category III is where we draw the line between

adult and pediatric research and where the threshold of risk-benefit requires that additional considerations be made to justify the research.

The conditions that need to be satisfied are presents a risk which is a minor increase over minimal, the intervention presents experiences commensurate with those inherent in expected or actual situation of the subject, the research procedure or intervention is likely to yield knowledge about the subject's condition which is of vital importance in understanding, and the consent of both parents is obtained.

[Slide.]

The fourth category is research that is greater than minimal risk without direct benefit, and the conditions of Category III cannot be justified. In this situation, the protocol must present an opportunity to understand, prevent, or alleviate a serious problem affecting children. Keep this category in mind because this, in turn, may turn out to be the category of research we are discussing today.

I will now move to discuss the current problems for IRBs when they consider pediatric research. Please

think about how these issues will be intensified when protocols involving normals and those without the disease under study are presented.

[Slide.]

The first question I ask the IRB community is: What issues are most problematic for reviewing FDA regulated pediatric protocols? The responses I received were as follows:

Many individuals commented that the use of placebos, especially invasive placebos, involving multiple shots for extended periods of time and infusions are still of great concern. The concern stems from the lack of benefit for the placebo group combined with a invasive procedure.

The second concern raised was Phase I trials. IRBs have become more comfortable with Phase I trials in oncology and AIDS populations, however, they still have significant concerns when Phase I trials are proposed in children with other disorders.

The problematic issue is the nature of the Phase I trials, the fact that it presents greater than minimal risk with no potential for direct benefit.

Incentives and payments continue to be of very large concern and the concerns are getting worse. IRBs frequently see proposed amounts well beyond compensation for expenses - the sum of the money, who receives the money, and whether children and parents should be told about compensation prior to agreeing to participate are commonly debated.

The IRB at Children's has insisted on several occasions that the amounts be reduced or the form of compensation be modified before a trial is approved. Not all IRBs will do this, and therefore, coercion becomes a large issue.

Another concern raised is contraception requirements. Although this is a particularly important issue, protocols may specify methods of birth control that may not be commonly used by adolescents.

I need to comment on the pressure at time as very problematic. Investigators constantly inform IRBs that approval needs to be granted quickly or else the center will dropped from the trial.

Appropriate time for review is essential for all research, however, issues of time may have the potential

to create even greater concerns in pediatric research. Ethical discussions, such as today's, need time and thoughtful consideration. A five- to 10-minute discussion at an IRB meeting may not be sufficient and cannot be expected.

Secondly, protocol are often developed to obtain study patients and results in the quickest manner possible. On several ethically challenging protocols before an IRB narrowing the eligibility criteria made a protocol ethically acceptable, however, the eligibility limitations required a much longer recruitment period and as a result, it took the investigator a longer period of time to complete the trial.

Many IRBs have commented on the need for guidance or information sheets addressing pediatric research. A pediatric research information sheet would assist IRBs in evaluating pediatric research and remind them of their responsibilities. This will become essential if IRBs are asked to review drug and biological protocols which include normal subjects and subjects without a disorder.

There has been some preliminary experience with

proposing the use in normal children in research with greater than minimal risk and no benefit. In a situation at my own institution, it was determined to be unacceptable and changes in the research protocol were required.

[Slide.]

I want to spend a minute on the concept of minimal risk although we will probably be discussing that a lot this afternoon, because this really is the basis of many IRB concerns.

The definition as provided in the regulations, the HHS regulations, are the probability and magnitude of harm or discomfort associated in the research are not greater in and of themselves than those encountered in the daily life or during the performance of routine physical or psychological examinations or tests. Easy to understand? Not really. This definition is, and continues to be, problematic for IRBs.

I would like to also read two sections of the official IRB Guidebook, a publication by OPRR.

[Slide.]

In the section under Children, it talks about

minimal risk and its, "Procedures that usually present no more than minimal risk to a healthy child include urinalysis, obtaining small samples of blood, EEGs, scratch tests, minimal changes in diet or daily routine, and the use of standard psychological tests."

[Slide.]

The guidebook then goes on to state, "The assessment of the probability and magnitude of the risk, however, may be different in sick children and may very depending on the diseases or conditions the subjects may have. IRBs may consider children suffering from chronic disease who are accustomed to invasive procedures are placed at minimal risk by involvement in similar research procedures, in contrast to children who have not had such experiences."

One might conclude that minimal risk may be considered differently for normal versus sick children, however, OPRR is also on the record for publicly stating that this form of relative risk is not a criteria that should be used in determining minimal risk in pediatrics. You can see why the IRBs are confused.

[Slide.]

These quotations led to the second question I asked the IRB community. "Do you have problems with the definition of minimal risks and minor increase over minimal?"

The quotes demonstrate the problems with deciding which research interventions may be considered ordinarily encountered and whether you can even apply the concept of relative risk. Even if relative risk is acceptable, this would certainly not apply to the use of normal children in some of the cases that we will discuss today.

Some IRBs do apply the concept of relative risk and are comfortable with this. Another comment was, "We have so much trouble determining what is considered minimal risk, therefore, it becomes impossible to think about what is a minor increase over minimal.

IRBs commented that often drug and biological protocols, an emphasis is placed on the physical risk, and not the psychological or emotional risk. How do you take into consideration risks associated with missed school or loss of sports practice? How about hospital admissions or trips to the hospital when they are not

normally required?

Often drug companies overlook these issues in developing pediatric trials, yet, I know of several protocols at my own institution where parents have refused to participate for just these reasons, and expected recruitment has been a problem and very much a disappointment for the sponsor, as well as the investigator. These things need to be thought about seriously.

IRBs often receive complaints about inconsistencies among different IRBs. This is certainly apparent in asking IRBs to classify pediatric risk. I personally do not find this a barrier and feel this determination is consistent with the concept of local or institutional IRB review.

[Slide.]

The last question I asked the IRB community was how they obtain a consent and what are their concerns. As expected, the responses I received are varied. In general, the age IRBs think children are capable of providing assent is between 7 and 8. The method of assent varies from verbal agreement to a signed signature

on a parental consent form, separate assent form, and some institutions even have different assent forms for different age groups.

IRBs commented that the determination as to whether a risk is capable often needs to be made on a subject-specific basis rather than a protocol basis. For example, there may well be a 10-year-old, because of maturity and emotional reasons, may not be able to provide assent. This is often not recognized.

Another issue raised is what is meaningful assent. It is easy to place emphasis on an assent form, and not the process. Children understand and process information in more interactive ways. Visual and interactive ways of communicating the research are desirable.

Showing a child the MRI machinery or using videotapes are just to name a few. We must pay greater attention to developing a meaningful consent and assent process. Many IRBs are just beginning to understand and address this issue.

The last issue raised, that assent is not always required when involvement in the research holds out the

prospect for direct benefit that is only available within the context of the research. In this situation, the parents' decision can override a child. In fact, many may argue that asking for assent in these situations can create unnecessary conflicts between parent and child.

There may be an obligation to inform the child, but not seek permission. This is a controversial topic.

[Slide.]

In conclusion, I have tried to think ahead about IRB reactions to research involving normal children and children without disease in drug and biological protocols. The issues I see are as follows:

1. What category of risk will these protocols fall under? The discussions we have later will put this concern into action. If they fall into Category IV, IRBs have very little experience with this category, and many will just say that the research is unacceptable.

2. Without guidance and better consensus about the definition of minimal risk, minor increase over minimal, and experiences commensurate with ordinary activities, I think some IRBs will become paralyzed with the type of protocol we are discussing today.

3. I suggest that FDA assist IRBs by providing a guidance document or information sheet. IRBs live by the information sheets that Paul Goebel's office have produced in the past.

4. There needs to be adequate time for debate and consideration. The fact that the subcommittee today is devoting the entire day to talk about these issues demonstrates the magnitude and concern and the need for thoughtful process.

This approach may be needed in the IRB community, as well.

5. Appropriate pediatric expertise on the IRB is essential. With the exception of the IRBs for pediatric academic centers, often pediatric representation on IRB will be one pediatrician or at the most one or two pediatric specialists. Is this really appropriate when we start reviewing the protocols discussed today?

6. As mentioned above, the assent process needs to be improved.

7. With the past year's history of institutions being shut down by OPRR, IRBs are scared and carefully

evaluating their practices for compliance with the letter of the law.

In OPRR's finding with several institutions, such as Duke University and the University of Illinois, there is reference made to the lack of conformance with the special protections for children. I personally was on one of these site visit teams and saw first-handedly the attention and scrutiny given to pediatric protocols that raised less ethical concerns than what we are discussing today.

I am not sure where this will lead and whether it will have an impact, however, my sense is that some IRBs may tend to be more conservative for at least the immediate time-being.

8. There is no question that we need to perform pediatric research on children, so they are not continued to be considered therapeutic orphans. However, we may need to realize that in some situations, we cannot apply clinical research methods accepted in adult trials to pediatrics.

As a result, it is possible that some studies just cannot be done. I must say that looking over the

list of cases to be discussed today, my first reaction is there is not way many of these would ever be approved before my IRB, however, I, as many IRBs, are committed to a process of thoughtful discussion, so that progress can be made in an ethically acceptable manner.

I also need to add that I am from a pediatric academic institution. I think about these issues on a day-to-day basis. I am concerned that IRBs without the expertise and depth of knowledge may be approached to approve these studies because maybe they may be less likely to bring up concerns and approve a protocol.

I look forward to learning from the discussions ahead of us, and I thank you for this time and opportunity.

DR. CHESNEY: Thank you very much for outlining the complexity from the point of view of the IRB. The concept of IRB paralysis is one that boggles the mind.

Our next speaker is Dr. Stephen Spielberg from Janssen Research Laboratories, who will be presenting the point of view of the Pharmaceutical Research and Manufacturers Association.

DR. SPIELBERG: Thank you, Dr. Chesney.

[Slide.]

I really greatly appreciate the opportunity that FDA has afforded us to look in some depth at many of the ethical issues involved in pediatric clinical trials. It is quite clear that with the increased activity that is now going on as a result of FDAMA and as a result of the 1998 Rule that PhRMA places an incredibly high priority on the ethical conduct of pediatric studies.

This is something that is an absolute underpinning of all that we should be involved in, and certainly supports the general principles set forth in the DHHS documents, as well, as the further enunciations and discussions in the American Academy of Pediatrics Committee on Drugs, and in the step two ICH E-11 document that deals specifically with pediatric research.

In the next few minutes, I am very quickly going to go through some of the basic outline of that new document in step two, to provide you a basis for the discussion subsequently of the issues of non-therapeutic research.

[Slide.]

It is quite clear that safe and effective pharmacotherapy in children requires clinical studies in children, and this basic principles needs to be continuously remembered in the context that not to do such studies places children at greater risk, and I don't need to go through that in depth now. Dr. Murphy has already outlined some of those issues, and I think most of you are familiar with previous therapeutic misadventures that resulted from not having the knowledge that we need how to use medicines in children safely and effectively.

This means that the ethical imperative to obtain such needed information is clinical studies has to be balanced against the absolute ethical imperative to protect each and every child in such studies.

This is where have struggled all through the years and where we continue to struggle, and if we are doing our job properly, probably must always continue to struggle.

[Slide.]

In the ICH document, we quickly review the role of the IRB as a critical protectant of children in

studies, the assurance of the scientific validity of studies, and the assurance that those studies are indeed written for children, and not simply adult studies with the age range changed on them, and the assertion that seems very obvious, but as we have heard already, may not be obvious in the United States, and certainly internationally has not been emphasized enough, that being that the IRB has to have members and/or bringing consultants knowledgeable in pediatric ethical, clinical, and psychosocial issues that all of those things have to be dealt with, and it is not just having a pediatrician on the IRB, but often nurses and teachers and even parent representatives who understand the lifestyle of children and what is and is not distressing or risky for a child.

[Slide.]

In terms of recruitment of participants, we talk about information which can be obtained in a less vulnerable population should not be obtained in more vulnerable populations. Clearly, anything that can be done in consenting adults to provide information about humans, after all, although children do differ from adults, we are the same species, and a lot of adult

information can be derived that is important in planning pediatric studies in children, and similarly, the studies in handicapped or institutionalized children limited to those diseases or conditions found principally or exclusively in those populations or where the underlying conditions of those patients would be expected to alter the disposition or pharmacodynamic effects of medicine.

[Slide.]

Clearly, we have talked a little bit about, and we will have opportunity to discussing later in the day, the issue of recruitment and retention of patients in studies in a non-coercive manner - the issues of reimbursement, and the issues of avoiding coercive inducements, and what those coercive inducements may or may not be in an individual setting, in a specific children's hospital, or in general.

The issue of distributive justice, an attempt made to recruit patients representing the demographics of the community unless there is a valid reason not to, that we all have both the opportunity to share in the benefits of research, as well as to share in the risks associated with that research.

[Slide.]

Consent of a minor, again, we deal with informed consent from the parent or legal guardian, that permission for the minor to participate in the study typically obtained prior to discussing the study with the minor.

We discussed briefly the issue of emancipated minors who are able to sign their own consents, and then the assurance that children are informed about a study in language and style--it is not just language as was alluded to--that are appropriate for their age, and that active, written assent obtained from children of appropriate intellectual age, determined by the local IRB, as is stated, typically around age 7, and of particular importance is that that assent includes the child's right to refuse to participate or withdraw from the study at anytime despite the fact that their parent has already consented and agreed that that child may be participating.

The things talked about from a child's vantage point and the documents in your handout by Bill Bartholme and others where it is from a child's perspective of his

or her own individual autonomy and control over the situation, and assurance that that is real, that an investigator will not proceed if the child says no, overridden under certain therapeutic trial situations again where a child's welfare would be endangered by not participating in a trial.

Now, we get to the issues of risk-distress and benefit, critical to the ethical conduct of any clinical study in a child is the need to minimize risk, to minimize distress, to maximize both direct and indirect benefit to each subject in a clinical trial, and thus, always to strive in doing any of our work, to optimize the risk and distress to benefit ratio.

[Slide.]

How do you minimize risk? I am thinking here primarily from an industry-sponsored study point of view where we are dealing with medicines under development, perhaps those already marketed for adults, or those being developed both for children and adults.

Understanding and utilizing all preclinical data and clinical safety data in adults, again, remember children are of the same species and that utilizing adult

pharmacokinetic data and safety data derived from adults is invaluable in planning the safe and effective study of pharmacokinetics and safety in children, in both single dose and in multi-dose pharmacokinetic studies.

Designing the studies to minimize the number of participants consistent with good study design and getting the data right. In pediatrics, we have often been guilty of doing studies in too few children, which we have underpowered studies and lack of usable information. Our literature is filled with that, and we have to avoid that, but at the same time we have to minimize the number of children who are exposed to studies and of procedures, and performing studies--this is absolutely critical--at centers experienced in clinical investigation and in the management of pediatric patients including in the management of pediatric emergencies should they arise during the course of an investigation.

[Slide.]

Minimizing distress. Designing protocols specifically taking into account the needs of children. We can no longer accept adult protocols with the age

ranges changed on the top of the page and subject children to fasting periods or time periods that are inconsistent with the lifestyle of a child in a family. The protocols indeed must be written in a child-friendly manner.

Even more important perhaps is the design of the clinical investigative centers, the same protocol conducted at different centers can produce very different levels of distress and very different levels of risk for children, and in order to minimize both the distress and risk, these centers have to be staffed with personnel knowledgeable in dealing with both the medical, as well as the psychosocial needs of children, and providing a comfortable, familiar setting with age-appropriate furniture, food, and play equipment.

This all sounds trivial, but some children are now being studied at sites that really do not provide these levels of comfort and convenience and distress reduction for children.

[Slide.]

Minimizing the discomfort of procedures. I think, as pediatricians, all of us know that the level of

distress provided by a procedure is almost entirely dependent on the expertise of the staff in dealing with that child, comforting that child, and being able to get blood on the first stick, and not having to do repeated venipunctures, absolutely critical.

Also, offering such things as topical anesthesia to place IV catheters to avoid the pain of catheter placement, and the use of indwelling catheters rather than repeated venipunctures, minimizing the volumes of blood that need to be drawn, and collection of research samples at the same time that routine clinical samples are obtained, again to minimize the blood volume, to assure that the catheter can continue to function, and that children will not have to have repeated painful procedures.

[Slide.]

In terms of benefit, the AAP Committee on Drugs discusses ethically permissible when it has been shown that a potential benefit to the individual child or to provide generalizable knowledge, and when potential benefits outweigh risks, and they construe benefits in a broad sense - direct benefit to the patient, advancing

knowledge of the disease or treatment, and something else that can be provided to the child in a study, that is, understanding by the child that he or she has contributed to the welfare of other children, a true benefit that can accrue to children participating in helping other children, as well as themselves in clinical trials, but it has to be done in an active sense.

[Slide.]

These are the DHHS categories. Again we are dealing with the issue here of greater than minimal risk with no direct benefit, but generalizable knowledge about condition or disorder, so-called non-therapeutic research.

Here, I will leave the ICH discussion and go on to non-therapeutic research.

[Slide.]

Almost by definition, most of our single dose pharmacokinetic studies to establish dose and safety, and to guide subsequent clinical trials are going to be non-therapeutic. However, from our history of pediatric therapeutics, nearly all the therapeutic disasters of the past have resulted from going on into clinical trials not

understanding the pharmacokinetics of drugs in children and therefore leading to overdoses, everything from chloramphenicol Grade AB syndrome on up and down the line.

That information is indeed critical to subsequent safe and effective pharmacotherapy and it is critical to subsequent clinical trials of efficacy in children.

It is typically performed in patients with the disease for which the drug was intended. This differs from most adult Phase I trials which are again done in normal volunteers. This increases the potential benefit to the individual patient, as well as to other children, and participants in such "Phase I studies" often end up being offered the possibility or are eligible then to participate in subsequent clinical studies or open-label use of the medicine earlier than might be available for other children, so that in this setting, benefit can be optimized.

[Slide.]

We talked about the issue of minimal risk or minor increase over minimal risk and the difficulties

that IRBs have, and that is clearly going to be one of our discussions - the nature commensurate with the patient's expected medical, psychological, social, or educational experience.

Is the single needle stick or placement of a catheter within the experience of most children going to the doctor? Perhaps, but certainly a bone marrow aspirate would not be except in children with cancer, who have having repeated bone marrows, in which case perhaps a bone marrow biopsy in the context of studying a new chemotherapeutic agent might be acceptable.

[Slide.]

Studying subjects, how do you optimize benefit? By studying subjects ultimately likely to benefit themselves from the medication, and then we will go on into some special considerations of the limited circumstances of healthy subjects.

But I would also like to point out that whether the child is a patient or the child is a healthy subject, the educational components about science and medicine, about altruism and how we really are all in the same boat on this planet, and how we can contribute to the welfare

of other children can be a major benefit to children.

[Slide.]

In a study at Children's Mercy Hospital in Kansas City--I hope I am not taking this from Dr. Kauffman--but it is an important study because indeed it looks at the issue from a child's point of view, and in all issues of consideration of distress and of risk, we have to think about it from a child's point of view.

This is a study of 5- to 16-year-olds participating in studies in what I believe is one of the best units for doing pharmacokinetic and pharmacokinetic/pharmacodynamic studies, 95 percent of the children said that they would participate in another study.

The main reason that they wanted to participate was a desire to help other kids and to increase medical knowledge. Altruism is alive and well in children.

The negative comments about the experience truly were minimal. Most of them complained about food in the hospital - rational, they know, blood drawing, but often not really a big deal particularly when it was done in the context of offering Emla and other topical anesthesia

and done by people expert in doing this. Once the IV catheter is in place, the children go and play in the playroom, play video games, play with toys, play with their peers, and periodically come back to the nursing station to have blood obtained through that catheter.

Sleeping overnight in the hospital, as was talked about, can be a distressing experience for children. It also can be a positive learning experience for children. It depends how it is done.

[Slide.]

Now, studying of healthy subjects. Just some initial thoughts. Children who are clinically stable with a chronic illness, for example, children with asthma, it may incur less risk and be less distressful to a patient to do a non-therapeutic pharmacokinetic study at a time that a child is not acutely ill, it may be.

It may be acceptable to study some medications for conditions for which that patient may be at increased risk, for example, some children with cancer, who may be in need of new antifungal therapy, they may indeed be the most likely to benefit from that new medication over time, may be an acceptable patient population, but still

must fulfill 45 CFR 46.404 or 406, the minor increase over minimal risk issue again as defined with some difficulties often by the IRB.

[Slide.]

What about normal pediatric subjects for discussion, again to fulfill these criteria, I would argue it should be for medications for illnesses likely to occur in normal children. We are not usually going to study medications for rare diseases, obviously, for cancer, for diseases where there can be studies in children with the disease in question, but again with extremely careful consideration of what this minor increase over risk means, data-driven approach from children about their perception of discomfort and risk, and data-driven from the science about the compound, what do we truly know about the risk of that compound in the human population before going into a pediatric population.

I would further submit this should be in children able to assent to participate, able to understand and perhaps thus able to gain additional benefits in terms of their understanding of what their

participation in such a trial does indeed mean.

[Slide.]

Minimize the requirements for non-therapeutic studies in younger children. This is a lesson I think to the agency, to us, and to investigators. Where studies can be done other than in the context of involving normal children, obviously, we should try for that, and this means an intelligent application of pharmacokinetic data and of developmental pharmacology principles along with the use of population pharmacokinetic studies in the context of therapeutic studies.

In other words, for example, understanding the pharmacokinetics and the mechanisms of clearance of a drug in older children able to assent, in younger children not able to assent, doing it in the context of therapeutic studies using population pharmacokinetics and our evolving knowledge of developmental pharmacology to understand what the right dose is, so that when that medicine is on the market, risk to patients, real patients is going to be minimized and benefit to real patients is going to be optimized.

[Slide.]

In summary, then, the existing guidelines really do provide us a great deal of information. The Academy of Pediatrics has expanded on this, the ICH documents have expanded on it. Several of the things in your package have expanded on it. Clearly, IRBs are still struggling with issues and we need to address those things up-front.

We need to assure that the standards that are detailed in these guidelines are involved in all studies of children and that these principles are set forth and are assured in all investigation of pediatric subjects.

We need to be sure to keep studies to a minimum consistent with obtaining critically needed knowledge and always ask ourselves is that study really needed to get the information to assure that when we are using that medicine in a therapeutic setting it can be used optimally.

Studies of clinically well or healthy subjects can I believe be done, but require truly an additional level of protection.

Thank you very much.

DR. CHESNEY: Thank you very much, Dr.

Spielberg. That was very, very helpful.

Our last speaker before the break is Dr. Ralph Kauffman from Children's Mercy Hospital in Kansas City, and I understand he is a member of the PPRU there, who will speak from the point of view of the investigator.

Investigator Comments

DR. KAUFFMAN: A number of the things I am going to touch on have been mentioned this morning, so I will try to move through them fairly quickly.

[Slide.]

Steve just mentioned some of the areas, the so-called non-therapeutic research occurs, and these are the areas that we have particularly been involved in, in the last few years, where an investigational drug is given to a child with the target condition, but in the pharmacokinetic studies, for example, no therapeutic intent in the study or the administration of an experimental drug to a child with a chronic condition, which is in remission, such as asthma, at the time of the study, so there is no expectation of therapeutic benefit, immediate therapeutic benefit, or the administration of an investigational drug to the normal child.

[Slide.]

The fundamental question here is are there circumstances under which it is ethical to include normal children in a study when they cannot fully understand or assess the potential benefits and risks, and from which they can expect no immediate drug benefit.

[Slide.]

The basic rights of children under the principles that we are all familiar with are no different than adults, however, it is the interpretation and the application of these principles in the context of this type of research that raises the fundamental questions.

When including children in clinical research, we have an obligation to take special care to assure that they are included in the benefits of research and, at the same time, they are not exploited or placed at undue risk, and this is the risk-benefit assessment.

[Slide.]

I am going to be very brief here, but I have to mention informed consent to set the context for some of my later comments.

This has to do, of course, with the principle of

respect for the autonomy of the child, respecting the rights of the child as a person, as an end and not a means, and we will discuss this more later.

[Slide.]

Probably the most important aspect of this discussion is how do we assess risks and benefits in the context that we are discussing today. Some have argued that children can never participate in research subjects unless there is a potential for direct and immediate therapeutic benefit regardless of how minimal the risk.

On the other hand, if the risk is minimal or slightly greater than minimal, as you have heard, and comparable to the risk the child might experience in everyday life, it can be argued that children could participate in non-therapeutic research if they might benefit in the future of there is potential benefit for the population represented by that child.

[Slide.]

This argument has evolved over the past 20, 25 years, and the evolution is reflected to some degree in the American Academy of Pediatrics Committee statements on ethical guidelines.

In 1977, in the summary paragraph of their statement, the Committee on Drugs of the Academy of Pediatrics said, "In general, the Committee on Drugs believes that it is not ethical to conduct studies which offer no benefit to the child subject."

Now, that is pretty clear.

[Slide.]

However, in 1995, Steve showed you part of this, that statement disappeared, and in its place we have a paragraph that says, "Research studies may be considered ethically permissible when they can be shown to have potential benefit to the individual or provide generalizable knowledge and when the potential benefits outweigh the potential risks."

[Slide.]

Benefits should be construed broadly, should take into account the importance of learning about a disease process or biologic function, providing innovative treatment for the subject's own benefit, and the understanding of the child that he or she has contributed to the study of a childhood disease or the biology of children, the benefit of participation that

Steve alluded to a moment ago.

So, the '95 guidelines from the Academy of Pediatrics do provide the suggestion or open the door to the idea that benefits may extend well beyond the individual therapeutic benefits from the investigational drug per se if carried out in a certain way and in the right context.

I would like to make several points regarding the broad interpretation of benefits and risks.

[Slide.]

In addition to the potential for children to anticipate future benefit from information derived from a study that I have alluded to, or for therapeutic benefit for a category of children, I would like to argue that as suggested, in the AAP guidelines, children at some age have the capacity to derive satisfaction and benefit from the experience and knowledge that they have helped others, that is, altruism, and that this experience, in and of itself, can be beneficial.

The experience of participating as a research subject also can be educational to the child if the context is structured to provide that experience, so do

children have the capacity to be altruistic and can non-therapeutic study or participation in that be educational.

[Slide.]

Steve showed you the study that was conducted last year at our center. I will show you some of the data.

[Slide.]

This was in 63 children, 5 to 16 years of age. It was a survey designed to understand the children's perception of their experience, not the adult's perception of the child's perception, and that is an important distinction.

Most of what we have read and heard over the years is our perception of what children perceive. We were surprised, frankly. The most common reason that kids gave for participating in non-therapeutic research--and most of these were pharmacokinetic studies--was, as Steve said, helping other children or contributing to new knowledge.

Incentives and compensation were mentioned about a little over a fourth of the time, and then other

reasons were given.

[Slide.]

What was the best thing about being in the study? Well, it was fun, whatever that means. Contributing to other kids or to new knowledge and the quality of the care interaction and the experience, but the point I want to make here is that the great majority of the kids identified this as being a positive or not a negative experience.

[Slide.]

What was the worst thing? A third of the children said there wasn't any worst thing. About a fourth of them identified issues of needle placement, which we expected this to be the dominant issue because all these kids had indwelling catheters for 12 to 24 hours.

They didn't like the food, as Steve said, and the medicine tasted bad, and the teenagers didn't like to be woken up at night do things--right, at 4:00 in the morning, right.

[Slide.]

So, I think that we have some preliminary

evidence that there can be benefits from participation in so-called non-therapeutic research apart from direct immediate therapeutic benefit. It also supports the argument that children can participate from an altruistic motive.

I would like to make a few additional comments about how we as a community view risk. The beginning premise whenever we discuss this, and the prevailing intuitive view, is that research is inherently risky and including children in clinical research invariably exposes them to increased risk, and sometimes this is true, but in fact, there is a persuasive body of literature that indicates individual subjects may actually benefit from, and be at less risk, when enrolled in a carefully conducted controlled clinical trial than when receiving untested therapies under uncontrolled conditions.

[Slide.]

In addition, we must consider in the context of risk assessment, the risks associated with not including children in research, and this has been mentioned this morning.

John Tyson, who is at Baylor, has made an eloquent case in a paper published about four or five years ago, that the use of unproven therapies, which is commonplace, as you know in pediatric practice, when conducted outside a controlled research protocol, increases risk and constitutes uncontrolled experimentation in the individual child.

He cites several dramatic example of how thousands of infants have been injured or died because experimental therapies were widely used without appropriate research to establish benefit or risk.

[Slide.]

The history of therapeutics in kids is riddled with examples even in the current day. So, there is significant risk associated with not doing research in kids. In fact, Dr. Barbara Schmidt from McMaster has an article in last month's--I think it is either Pediatrics or Journal of Pediatrics--showing that infants in a placebo arm of a study had significantly better outcomes than those who were not enrolled, but were matched, but elected not to enroll in the trial. The placebo patients did better than those who didn't participate.

[Slide.]

I want to make a couple of comments about risk from my perspective as an investigator, additional comments. There are two aspects of risk that I don't want us to forget today as we discuss this, and that concern me most.

The first, I have already alluded to, and that is the risk to the general population of children associated with widespread use of unproven therapies outside the ethical oversight and scientific rigor of carefully controlled clinical trials.

The second is the rapid emergence under the incentives and pressures of FDAMA and soon upon us the '98 Pediatric Rule, of pediatric research being conducted by research organizations and investigators inexperienced in pediatric medicine, in pediatric ethical issues, and clinical research, who are involving children in clinical research protocols, many of which are non-therapeutic, without any cognizance or recognition of the ethical issues involved. I believe this presents one of the greatest risks of exploitation of children that we currently face.

[Slide.]

In our own experience, having said all of this, we are still evolving, but this is what we currently are using at our place to guide us in designing or accepting participation is various protocols, and our IRB currently pretty much works on these guidelines, too.

We have included subjects who are capable of giving assent, at least having some input into the decision to participate. In all the protocols, there has been substantial adult safety information available to us at the time we started the pediatric Phase I or II studies.

In the judgment of the IRB, the study has involved only minimal or only slightly more than minimal risk, and I acknowledge the problems in defining those, and in these cases, there has been potential benefit or future benefit to these subjects or a general benefit for the population represented by that subject.

These have included new asthma therapy drugs, new anti-asthmatic agents in children with a history of asthma, but who are physiologically normal at the time of the study, pharmacokinetic or bioavailability study of an

antibiotic that potentially could be used by the child and other children in the future, or the sibling of a diabetic who has a 10- to 20-fold higher probability of developing diabetes and may benefit from a diabetes study in the future.

We have declined to participate in some trials that we thought could not ethically be conducted, for example, a pharmacokinetic study in normal children of a cardiovascularly active agent that we thought the unknown risks or even the known risks were excessive for inclusion of normal children.

[Slide.]

So, I submit that there are situations in which non-therapeutic research, some of which may include normal children, can be ethically done, not in this situation, but here, a group of kids with their IV's in, playing on the merry-go-around in our playroom, who are making this a positive experience and also contributing to the welfare of others.

So, as we discuss these issues today, I hope we will keep the benefit and risk issue considered in its broadest sense, and not repeat some of the mistakes we

have made in the past.

Thank you.

DR. CHESNEY: Thank you very much, Dr. Kauffman, very, very interesting.

We do all have microphones on now, so I think we would like to have everybody go around the table and introduce themselves. Maybe we can start at this end, and if you could give your name and affiliation, and also for the benefit of other people in the room, whether you are a member of the subcommittee or a consultant or guest.

Introductions

DR. WALTERS: My name is Leroy Walters. I am from the Kennedy Institute of Ethics at Georgetown University, and I am a non-voting guest at this meeting.

DR. EDWARDS: Thank you. I am Kathy Edwards. I am a pediatrician from Vanderbilt University. I am a member of the committee.

DR. KAUFFMAN: I am Ralph Kauffman from Children's Mercy Hospital, Kansas City, Missouri. I am Director of Medical Research there. I am a non-voting consultant to the subcommittee representing the American

Academy of Pediatrics.

DR. NELSON: I am Robert Nelson from Children's Hospital, Wisconsin and the Medical College of Wisconsin. I am a pediatric intensive care physician and chair of the IRB there, and I am a voting member of the committee.

DR. O'FALLON: Judith O'Fallon, biostatistician at the Mayo Clinic, and I am a member of the committee.

DR. RODVOLD: Keith Rodvold, University of Illinois at Chicago, Colleges of Pharmacy and Medicine. I am a member of the committee, and I am the consumer representative for the committee.

DR. LUBAN: Naomi Luban. I am a pediatric hematologist/oncologist from Children's Hospital and George Washington University School of Medicine, and I am a member of the committee.

DR. SZEFLER: Stan Szefler from Denver, Colorado. I am the Director of Clinical Pharmacology at the National Jewish Medical and Research Center where we have a focus on childhood asthma and also I am one of the principal investigators for the Denver site for the pediatric pharmacology research unit network.

DR. SPIELBERG: I am Stephen Spielberg. I am

head of Pediatric Drug Development at Janssen Research Foundation. I am a non-voting consultant member representing PhRMA.

DR. FINK: Bob Fink, pediatric pulmonologist at Children's National Medical Center, Washington, D.C. I am a voting member of the committee.

DR. HUDAK: Mark Hudak. I am Chief of Neonatology at University of Florida at Jacksonville, and voting member of the committee.

DR. SANTANA: Victor Santana. I am a pediatric oncologist at St. Jude's Children Research Hospital in Memphis, Tennessee. I also serve on the FDA Advisory Committee for Oncologic Drugs, and I am a voting member of this committee.

MS. PETERSON: I am Jayne Peterson with the FDA, the Advisors and Consultants Staff, acting as the Executive Secretary for the subcommittee.

DR. CHESNEY: My name is Joan Chesney. I am in the Department of Pediatrics at the University of Tennessee at Memphis, and a voting member.

DR. DANFORD: I am David Danford. I am a pediatric cardiologist at the University of Nebraska

Medical Center in Omaha, and I am voting member of the committee.

DR. BOTKIN: I am Jeff Botkin. I am a general pediatrician from the University of Utah and Primary Children's Medical Center.

DR. GORMAN: I am Richard Gorman, a pediatrician in private practice and a voting member of the committee.

DR. CLAYTON: I am Ellen Clayton from Vanderbilt University, and I am a guest of the committee.

DR. WARD: I am Bob Ward from the University of Utah, a neonatologist. I represent also the American Academy of Pediatrics Committee on Drugs and direct the Pediatric Pharmacology Research Program at the University of Utah.

DR. FOST: I am Norman Fost, pediatrician and Director of the Medical Ethics Program at the University of Wisconsin, and chair of the IRB there.

MS. KORNETSKY: Susan Kornetsky from Children's Hospital in Boston, and I am a non-voting consultant representing the IRB community.

DR. KODISH: I am Eric Kodish, pediatric oncologist and principal investigator for Children's

Cancer Group at Rainbow Babies and Children's hospital in Cleveland, and a faculty member at the Center for Biomedical Ethics at Case Western Reserve, and I am a guest, non-voting.

MR. RACKOFF: My name is Jonathan Rackoff. I am a fellow with the Department of Clinical Bioethics at the NIH, and I am a guest.

DR. WILFOND: My name is Ben Wilfond. I am a pulmonologist at the NIH, and I am a guest.

DR. MURPHY: Dianne Murphy, Associate Director for Pediatrics at CDER-FDA.

DR. CHESNEY: Thank you very much. We are running pretty close to time, but we do need to provide five or 10 minutes at this point to ask anybody at the table if they have specific questions about the material presented.

Are there any questions for any of the speakers? Yes.

Questions and Comments from the

Advisory Subcommittee

DR. FINK: This is a general question I guess that the ethicists may address, that if you have a study

that has greater than minimal risk with direct benefit, but is placebo controlled, is that ethical for those patients who will be assigned to the placebo group?

DR. FOST: I am going to be talking about that at some length, if you want to wait.

DR. CHESNEY: Are you willing to wait?

DR. FINK: Yes.

DR. MURPHY: I also wish to state that at the next meeting that we will have on ethics will address the issue of placebo-controlled trials in children, so I think it is a very big, broad issue just so people will know.

DR. CHESNEY: Yes.

DR. FINK: This is Dr. Fink again. One other question. It seemed like there was a presumption that it was more ethical to involve individuals in non-therapeutic research who had the disease, the drug under study would potentially contribute to, but I would wonder, as a pediatric pulmonologist, asthmatic patients already bear a high disease burden and in the sense of fairness, isn't it maybe better to involve the general pediatric population in the study of drugs for the

treatment of asthma rather than those children already burdened with asthma?

DR. WILFOND: I will be addressing that in my talk.

DR. CHESNEY: Yes, Dr. Gorman.

DR. GORMAN: This is to Dr. Goebel. You mentioned MPAs for Children's Hospitals. Do the DHHS requirements for Subpart D also apply to Single Project Assurance numbers or Single Project Assurances for ambulatory studies?

DR. GOEBEL: No, they do not. The Single Project Assurances generally do not include a provision that the assurance has to apply to all studies done at the institution, whereas, the MPAs usually do.

DR. CHESNEY: Yes.

DR. WARD: As a neonatologist, linking the involvement to assent continues to leave the neonate as a therapeutic orphan, and if you go down the therapeutic misadventures that litter our pediatric history, the neonate has been the predominant player in those.

Steve, Ralph, Dr. Kornetsky?

DR. CLAYTON: Well, I can say that I am going to

talk a little bit about that issue. One of the points that I will say in anticipation of that is that it is fairly clear that if we insist on assent, and if insist on parental permission, then, in fact, there are studies on neonates that absolutely aren't going to be done.

One of the issues that I am going to raise is that there may be--certainly not under the current regs--but there may be times when it may be necessary to do these studies without assent even with the idea that we really do need to understand something more about what we are doing with little kids.

I mean I absolutely am sympathetic with what you are saying.

DR. CHESNEY: I have one question for Dr. Kauffman that I don't think any of the ethicists are going to raise. I am intrigued by the possibility of doing studies with groups of children, and you showed a group on the play equipment.

Have you done groups of children simultaneously?

DR. KAUFFMAN: Yes, we have. In fact, the picture, it just happens the picture that I had available, that I showed, was a family of four or five

siblings who came in at one time and did the study together.

On another occasion, talking about an altruistic experience or educational experience, on another occasion we had six children in at one time in the unit. There were ill children, hospitalized children in an adjacent area of the hospital, and a part of the activity of those kids while they were in for 24 hours doing their PK study, was to work with the child life people to work with the sick kids to do some activities with them. This was a very positive thing for both the ill kids, as well the kids participating in the trial.

So, yes, we have done up to six at a time on some occasions.

DR. CHESNEY: It raises a number of possibilities for classroom projects, and so on.

DR. EDWARDS: As an Associate Director at the Clinical Research Center at Vanderbilt, we are finding that a number of centers have been linked, adult and pediatric, for many years, and a number of centers that were not linked had both an adult and a pediatric unit are being combined, and I think one of the things that

might be very helpful for Dianne or other people from the FDA to talk with the people that are in charge of the CRC Networks to remind them that pediatric environments are very important and certainly the slides that Dr. Kauffman showed, because where we are in austere financial times and combining centers, it is really important that there still is a very unique pediatric perspective in those situations.

Dr. Kauffman, you are a unique pediatric free-standing and don't have adults.

DR. CHESNEY: It also raises the possibility of having a teacher go with the children and the parents go with the children, and whole groups from churches or whatever go.

Any other questions before we move to the break?

[No response.]

DR. CHESNEY: All right. Why don't we break, and if we could be back by quarter after 10:00, because we do have a full morning with our ethicists speaking.

Thank you.

[Break.]

DR. CHESNEY: We are ready to begin the second

session. We didn't forget the time, but the microphones had to be rehooked up, so I hope you enjoyed the extra few minutes.

We are going to start for the next 15 minutes by having Dr. Murphy present the case studies that she would like us to discuss in detail this afternoon, and then we will introduce the ethicists to you.

Presentation of Case Studies/Questions

DR. MURPHY: Thank you.

Again, we will not be discussing these. These are to refresh your memory for the committee and for those in the public who have not seen these cases, to let you know the actual situations which we will be discussing, so that you will have these in mind when our experts are presenting their discussion.

1. A manufacturer wishes to taste test a new elixir formulation of an antibiotic that has been approved for use in adults. The intended study population is asymptomatic, healthy children. The study design is to provide each child with a single dose of the antibiotic, observe for one hour and record reactions. For children who are capable, a short questionnaire about

taste tolerance and palatability will be given.

The questions that will be addressed to the committee are:

A. Does the study exceed the threshold of a "minor increase over minimal risk"? The issue that everyone finds so difficult, you get to decide this morning.

B. Would any precautions or exclusions minimize risk?

C. Could this study be performed in children who cannot give assent (under a certain age)? We are trying to get at the age issue here.

D. Would it make a difference if the children had a disease potentially responsive to this therapy? As you will remember from your letter, even though the discussion is about children who do not have the disease, we want you to reflect upon how that would or would not change each case.

E. Would it make a difference if this were an investigational drug, and the issue here that we are asking you to think about is the fact that if this is not already approved in adults, we have much less experience

with this product.

So, you are now changing the database upon which you are going forward, it is less as you will be studying this product.

The second case, please.

2. A sponsor has developed a new formulation of an anticonvulsant approved for use in adults. The intended study population again is asymptomatic, healthy children. The study design is to provide each child with a single dose of the anticonvulsant, observe, and obtain one or two blood samples for participation in a population pharmacokinetic study.

A. Does this study exceed the threshold of a "minor increase over minimal risk"?

B. Would there be any precautions that would minimize this risk?

C. Could this study be performed in children who cannot give assent? The age issue.

D. Would it make a difference if the children had the disease?

E. Would it make a difference if this were an investigational drug product?

On this one, we have made it even a little harder, because we have, as I keep saying, these are real cases, and we are trying to be efficient, so we are rolling sometimes a couple of situations into one.

F. If the pharmacokinetic design was to obtain samples at 1, 2, 4, 6, 8, 10, 12, 18, and 24 hours, would you allow the study to proceed or place any restrictions on the study?

G. And then Question G. Would your answers to A through F be different if the formulation under study were an antihistamine instead of a anticonvulsant? Here, we want you to address the severity of the disease.

Next, please.

3. A sponsor has developed a new formulation of an ophthalmic agent approved for use in adults. The intended study population is asymptomatic, healthy children ages 3 to 8. The study design is to provide each child with a single dose of the ophthalmic agent in their eye, observe them for two hours for adverse events, and if no adverse events are noted, then, they are to continue in this trial for a multi-dose 6-week study. It is not known if such agents would have any unique impact

on visual acuity in this age group where visual acuity is still developing.

We will be asking those four sets of questions that were in the prior two questions about "minor increase over minimal risk," how do you minimize the risk, would you make a definition by age or define who would be in these studies, or would it make a difference how much information you had if this product had not already been approved in use in adults.

4. A sponsor is developing a new MRI contrast agent and wishes to test safety and tolerance in children. The study design is to administer one dose of the intravenous contrast agent to hospitalized children with indwelling catheters, or who have previously established intravenous access, and observe the children for two hours.

In this situation, we are asking the same questions, and this population is obviously a population that is coming into the health care system for a reason. How does that change how you look at this? Answer the same questions A through D.

E. Now, would your answers to A through D be

different if the children were being admitted for placement of drainage tubes, so we have really changed the scenario for your last question, but it is children who are coming in, the theme here is children who are coming into the health care system for something, procedure. The second procedure is that they are going to come in and have PE tubes placed, and instead of a new MRI agent, an investigational antibiotic will be given prior to surgery, and there will be subsequent sampling of the middle ear fluid, which will be obviously coming out when they put the PE tube in, natural forces, nothing that will be done to the child to obtain that fluid except aspirate it, and they would obtain the serum sample.

How would that change your answers A through D?

5. Then, final question. What is the impact of compensation on parent/child permission/assent?

A. Would compensation unduly influence a child's assent? You have heard some of that discussion already. We want to make sure that that is specifically addressed at the end of this and how we looked at our prior cases. The specific question here is should a

child be aware/told of compensation prior to giving assent, if they are at the age to give assent?

B. Does compensation compromise a parent's permission to allow participation of their child in a clinical trial? Again, many of these issues have been previously discussed, and the National Commission has talked about these, but we want you to answer these questions in the context of these are the types of studies that we are receiving, and how would the nature, amount, and recipient of the compensation affect this decision?

We look forward to the committee addressing these and to help you, we have asked our panel of experts here to address specific components of this risk-benefit ratio, and I have asked the speakers who are going to address these issues to provide a sentence or two to you about what they think in their background, why we asked them to speak, if they think there is something you need to know in addition to the fact of what their institution was from whence they came. So, instead of my doing that, I asking you all to do that.

Thank you very much.

DR. CHESNEY: Thank you, Dianne.

We have six speakers and each individual will speak for 15 minutes. Then, there will be 5 minutes for the people at the table to ask questions, and as a former mentor of mine, Dr. Fost once said of pediatric ethicists--of ethicists in general, excuse me, if they were laid end to end around the world, it would be a good thing.

Let us start with Dr. Botkin from the University of Utah, who will speak to us about the history of research in healthy children.

Topic Presentations

Research on Healthy Children: History

DR. BOTKIN: Thank you.

[Slide.]

As I mentioned earlier, I am a general pediatrician. I am also somebody who has been involved in medical ethics for a number of years, a member of our IRB at Primary Children's Medical Center, and a couple of years ago had the opportunity to be a consultant for the President's Advisory Commission on Human Radiation Experiments. I am going to talk a little bit about some

of that experience and some of the issues that that review raised.

Now, my initial task was to talk a bit about history, but since I have a whole 15 minutes, I thought I thought I would add an ethical foundation, as well.

[Slide.]

The history is going to provides a couple of points. First of all, I think there is not much public controversy right now, at least that I have been aware of, about experimentation with children. This has not always been the case. We live in an era in which the Princeton offices of Peter Singer are being picketed, we have got folks quite concerned about genetically modified foods, a number of issues in science that are quite controversial publicly, but I don't think a whole lot of controversy emerging around pediatric research.

I think there is probably at least three potential reasons for that, maybe that the public and the profession and generally aware of contemporary standards and practices, and are comfortable with those.

Secondly, the public and profession perhaps have concerns. but these haven't arisen to the level of public

debate, or, thirdly, the public is oblivious to research in children unless it involves them personally.

Now, this has not always been the case. In the background piece that we were provided by Lederer and Grodin, concluded in their last paragraph, "The history of pediatric experimentation is largely one of child abuse."

I think that may be a little bit of a broad brush assessment of the situation, but the point being that the public has not always been oblivious to these issues in the past, I want to raise just a couple of points about where we have been over the last 100 years or so.

[Slide.]

Most of the controversy in the past has focused on research with healthy children or children affected by conditions unrelated to the research itself.

There were a series of experiments by Arthur Wentworth in 1896, in which he conducted lumbar punctures in healthy children, and the point of this was to understand normal physiology and understand the risk of the procedure itself.

Well, this exploded into the public consciousness and folks were highly concerned about use of children in this context. A number of states, and even the Federal Government, over the subsequent decade attempted to pass legislation that would have prohibited pediatric research. Now, none of these bills were successful, but it illustrates the nature of the public debate at the time.

Now, the issue has waxed and waned to a large extent over the 50 years, and as I mentioned, at the present time there doesn't seem to be much public controversy about it.

Now most of the debate in the past has focused on vaccine research, and I think that this controversy raises some basic questions about the definitions of the terms that we are using, such as healthy children in particular.

In past generations, healthy children were at high risk for developing infectious diseases and, as such, were the obvious candidates for experiments on preventative vaccines. That is less of an issue today with infectious disease although, of course, it is still

with us, but perhaps an analogous population would be children who would be at high risk for conditions based on genetic background and do we wish to consider these kids simply as healthy children or are they a different classification that bears additional thought.

[Slide.]

Now, despite periodic controversy, no standards were developed pediatric research really until the Declaration of Helsinki in 1964. Following World War II, the academic medicine had gained quite a bit of new prominence and there was a rapid expansion of research enterprise including research with children.

A particularly promising line of research was funded by the Federal Government in the postwar era, was research with radioisotopes. The ability to tag various substances and metabolites led to a wide range of experiments in children devoted to understanding normal physiology.

[Slide.]

As a consultant to the Advisory Committee on Human Radiation Experiments, we reviewed a large number of non-therapeutic protocols with children, and there

were a couple of themes that emerged from that review, and these were experiments that were conducted from 1940's through the 1970's.

First of all, there was a systematic underestimation of risk. Investigators explicitly considered the exposure to radioisotopes to be entirely harmless and these were based on false assumptions about low level radiation and about specific organ sensitivities to radiation.

Secondly, there was a systematic use of children in institutions or children hospitalized for other health conditions, either as subjects or as controls, and there was three-fold justification for this at least.

One was that the kids were in a controlled environment, investigators could tell exactly what the kids were eating and drinking. Secondly, they certainly were a population of convenience, they were at hand, and, of course, in that era, there was much less involvement of parents in the day-to-day care of children in the hospital or institution, so there was much less oversight that parents might exert on what was done with the kids.

Thirdly, there was a sense of reciprocity.

These were ward patients, non-paying patients in some circumstances, who were thought to be paying their way by participation as research subjects.

Lastly, permission from parents was not documented. Now, the Advisory Commission was unwilling to criticize past practice in this respect because basically, these research protocols didn't have evidence one way or the other about consent, but I think the oral histories that were obtained as part of the project, as well, clearly illustrated that consent simply was not a common practice at the time.

Now, there was a particularly enlightening exchange that I want to briefly give to you, that was part of a Law and Medicine Institute project in 1963, and they brought together some senior pediatric investigators at the time, and the explicit purpose was to talk about ethical issues in pediatric research.

I want to offer an exchange between a couple of physicians, at least one of whom is still quite prominent in the field. Dr. G says, "I might present a specific case of my own. We wanted lumbar punctures on newborns. This study would not be a benefit to the individual, it

was an attempt to learn about normal physiologist."

Dr. D says, "I would okay lumbar punctures. It seems to be a safe enough procedure if handled properly."

Dr. Y asks, "Did you ask permission?"

Dr. G. "No, we were afraid we would not get volunteers. We used ward patients only, thank God."

Dr. N says, "We have given various procedures, such as fluoroscopy studies also, and this has never been questioned. We have done 1,000 things with an implied feeling. Where there is some benefit somewhere, we wear two hats."

Now, the final report from the Law and Medicine Institute concludes, "Although parental consent is a necessary part of clinical research with children, it is not necessary, practical, or desirable to inform parents in detail about the research aims and procedures as long as the degree and nature of risk to the child is explained."

Now, I raise these historical examples not to sort of shake our heads over predecessor's practices, but to illustrate the divergence of opinion that has existed and may exist again over the use of the healthy children

in research.

The public at the turn of the century was scandalized at Dr. Wentworth's projects involving lumbar puncture is healthy children, yet, we see 65 years later, physicians doing the exact same thing using that they had done 1,000 things, in ward patients only, thank God, with an implied feeling.

So, I think in medicine we obviously have to be careful about trying to broaden our perspective and understand the public perception of what it is we are justifying in the conduct of this work.

[Slide.]

Now, what I want to do is address the specific question: What is the justification of exposing healthy children to any risk, discomfort or inconvenience?

I think there are several potential justifications for this that I want to walk through quickly.

[Slide.]

The first is, in fact, that non-therapeutic research with children is not justified. This was the position of Paul Ramsey highlighted in the famous

exchange with Father McCormick back in the 1970's.

For Ramsey, progress in medicine was not the highest good. He argued for the fundamental principle in the Nuremberg Code, that the voluntary consent of the subject was essential to the ethical conduct of research, at least in research conferring no benefit to the subject, and according to Ramsey, children and others incapable of consent could not be used for the benefit of others.

[Slide.]

Now, turn to five different ways we might think about justifications for non-therapeutic research.

The first hinges on a certain imprecision in the definition of healthy, and I think we have seen actually each of these reflected in the comments already this morning, and I also note that they are not mutually exclusive by any means.

So, the first one hinges on a certain imprecision in the definition of healthy and in the definition of non-therapeutic. We are all at different levels of risk for future disease. For those at greatest risk of disease, we might justify their inclusion in

research in the hope that benefit will accrue to those very children by advancing medical knowledge in the prevention of disease, and obviously, vaccine research, potentially, some genetic research would fall under this category.

The second potential justification also hinges on an indirect benefit to the child subject. This rationale suggests that participation in research fosters altruism in children through their recognition of needs in the community and their self-sacrifice in addressing those needs. Research participation contributes to the moral development of the child and is thus a benefit.

Clearly, this justification works well for older children who are old enough to understand the basic aspects of the research and to give a sense of participation, and clearly, forcing altruism on children may not foster much moral development.

So, this justification would not permit non-therapeutic research on children younger than perhaps the seven years of age.

[Slide.]

The third justification is a bit broader. It

suggests that if children could consent to research, they would do so as long as its burdens were small and the benefits to others were significant. Many adults consent to research, and so the rationale goes we can assume that many children would consent, as well.

Perhaps this is what Dr. N meant in the Law and Medicine project, when he said that things were being done with an implied feeling. Perhaps the infants were implying that they would participate with the research.

The difficulties with this argument are transparent. With adults, we have a track record on which to base a substituted judgment if they are too ill to make decisions for themselves. We have no basis on which to assume that a young child would consent to anything in particular, much less research involving a level of risk.

[Slide.]

The fourth potential justification is also rather broad. It suggests not that children would consent, but that they should consent, and this is the basis of Father McCormick's argument in the 1970's. Children as members of the human community receive

benefits from their community, and therefore, should contribute to that community through participation in medical research when they have the opportunity to do so.

In addition, obligations of the child may be strengthened by the unique position children are in to help other children, however, the extent of any such obligation is not transparent. If children do have this obligation, is the obligation specifically to other children, or is it a broader obligation to benefit all other members of human society.

If the obligation is limited to the promotion of the welfare of children, then, clearly, the kinds of research that should be approved are limited. We might imagine that in the future, children might be found to be an excellent source of stem cells for the treatment of adult diseases. Should that be approved or should it not?

While this justification is attractive, there are at least several serious problems with it. First, as Ramsey argued, it afford moral agency to children who are not moral agents.

Second, children have not voluntarily accepted

the benefits of society, therefore, it is unclear whether they should be awarded moral obligations to reciprocate, particularly when there is personal risk involved.

Third, I think one of the most critical is that our society has not guaranteed health benefits to children. In this context, children are not guaranteed access to pharmaceuticals. It would be inappropriate to assume that all children have obligations to society to put themselves at personal risk when society does not feel an obligation to provide the fruits of research to all children.

So, these concerns suggest that if this justification is used, it may be the more advantaged children who should be recruited for research including those who have access to health care and perhaps those who are already using the health care system.

[Slide.]

Lastly, the fifth potential argument is broader still. It dispenses with the conundrums of what children should or would do and simply states that children are useful as subjects of research.

Children may not have obligations to others, but

we, as adults, do including obligations to our children, to our patients, and to our future children. In order to fulfill our obligations, the argument would go, we need to use some children for the benefit of others.

Now, to some extent, to a significant extent, this is sort of a guinea pig rationale and despite our discomfort at the notion, I suspect it has been the predominant rationale for investigators through the century.

This argument violates the categorical imperative that people should not be used as means only. Nonetheless, I think the Advisory Committee on Human Radiation Experiments had this justification in mind when it concluded, "As important as it is to promote the welfare of children as a class, this interest justifies only minor infringements on the principle not to use children as mere means to the ends of others."

So, the Radiation Committee was clearly and explicitly saying this is a minor infringement of an established moral duty.

So, this obligation hinges on our obligations to the sick, but, of course, we also have strong obligations

not to harm others, and many ethicists will claim that our duty not to harm the healthy is stronger than our duty to aid the sick.

If this is so, then, use of healthy children requires that we avoid harming them in the process. This justification suggests what we must interpret minimal risk language very conservatively. Harming a child while using her as an instrument for the welfare of others would be a significant moral transgression.

Now, the Declaration of Helsinki concludes by stating, "In research on man, the interest of science and society should never take precedence over considerations related to the well-being of the subject."

[Slide.]

So, I don't think that there is any social consensus that I can tell on the justification for the participation of children in non-therapeutic research, and the right justification certainly is by no means obvious to me. I think all of these justifications have difficulties and limitations.

The lack of clarity in the resolution of the debate has fostered I think this minimal risk standard as

a compromise between our discomfort in the use of children in research and the therapeutic imperative.

Recall, for McCormick, who was an advocate of the use of children in non-therapeutic research, minimal risk meant interventions analogous to a cheek swab. So, now as we routinely go beyond research or at least considering going beyond research risk analogous to cheek swabs in healthy children, I think some additional discussion and clarification about the justifications that underpin this enterprise are warranted.

Thank you.

DR. CHESNEY: Thank you, Dr. Botkin.

Are there any questions from the members of the committee? Yes, Dr. O'Fallon.

DR. O'FALLON: Your use of the word "conservative," to me it has got a whole wide range. I would like you to pin that down for me a little bit bitter.

DR. BOTKIN: It means basically a low level of risk, that minimal risk would indeed be something analogous to psychological studies, cheek swabs, physical examinations, the sorts of risks that may entail

extremely low levels of concern about long term or immediate effects.

DR. CHESNEY: Yes, Dr. Walters.

DR. WALTERS: Jeff, would you advocate equal treatment for children and adults in the sense that there may be some circumstances where it would be morally justifiable to conscript adult or at least to do research on adults without their consent because it would be useful to society?

DR. BOTKIN: No, actually, I wouldn't advocate that although I think that is exactly where the argument of utility would go. Now, maybe it would justify research that would involve the sort of things that are exempt from some IRB review, like public observation of behavior, collection of publicly available data, et cetera, that may involve some small level of risk, but for which consent is currently not considered mandatory.

So, I think that is indeed a specific concern of using that justification in children, is that implication for adults.

DR. CHESNEY: Thank you very much. I think we are ready to move on to the next speaker, Dr. Norman

Fost, from the University of Wisconsin at Madison, who will talk to us about the concept of benefit in pediatric research.

Benefit in Pediatric Research

DR. FOST: Thank you. I would like to especially thank Ben Wilfond for help in organizing this and in framing some of the issues. The line that Joan Chesney attributed to me was actually stolen from James Childress, and I would like to steal another line from James Childress who, when asked to confront a lot of tough issues in 15 minutes, said he was going to adopt the style of Hubert Humphrey, who talked at 500 words per minute with gusts up to 1,000. I am going to do that also.

I am going to restrict my comments or ask you to assume that my comments are only talking about children who can't assent, because I think that is the most difficult issue, and if we could justify non-therapeutic research in those children, then, it would be a lot easier with children who are older.

Second, I am going to focus on the two issues that Susan Kornetsky said were the most troubling in her

survey of pediatric IRBs, namely, Phase I studies and placebo-controlled trials. I know the focus of this session is supposed to be on non-therapeutic studies in healthy children, but that is one of the central questions, is whether a Phase I study should be considered as therapeutic or not and whether a placebo-controlled trial can be considered as therapeutic for the children who are in it.

So, I am going to focus on those because in the limited time, I think those are the crunchy issues.

[Slide.]

So, I am going to say a few things about types of benefit, some comments about Phase I studies, placebo-controlled trials, and then if time allows, refer to three kinds of randomized trials in which these questions arise.

[Slide.]

The types of benefit obviously include societal benefit. These are questions of design which I don't think we need to cover here. There can obviously be a direct medical benefit if a child is receiving an experimental drug in a placebo-controlled trial.

There are indirect benefits, such as subsidized care, and that is not just saving some money for the parent of the family, sometimes it is the difference between care and no care. In a country with 43 million-plus uninsured, a third of whom are children, being in a trial may mean getting some medical care where otherwise you get none.

Gifts and monetary rewards seems to me are not--well, I will come back to it, but those are obviously other indirect benefits, I will say a few words in a minute.

There is the psychological satisfaction of altruism, of contributing to a trial, of contributing to others. I will come back to that.

Finally, there are just benefits of being in a trial even if you were going to get care otherwise, namely, patients in a trial are usually guaranteed a certain level of physician expertise. You have to have certain credentials to be running a trial. There has to be a literature review to enroll somebody in a trial.

There is peer review at multiple levels, at the grant process, the IRB review, the anticipation of

scrutiny of editors, and then, of course, the ongoing monitoring for toxicity and efficacy as the trial is going along, and sometimes the additional protection of a data safety monitoring board.

So, somebody in a trial, as Dr. Kauffman alluded to, may be getting much better care because of all these indirect benefits.

[Slide.]

A couple comments about monetary rewards. Obviously, we should distinguish rewards and incentives, on the one hand, from reimbursement for expenses, which raise, reimbursement to me raise no serious ethical issue, but I think the concern is about undue rewards.

I think it should be self-evident that parents shouldn't profit by exposing their children to risks. The question is whether the risks are worth the rewards for the infant, and my comments here are mainly about those children too young to assent. It is high speculative, that is, the notion that down the road, a couple hundred dollars or a gift certificate, the child will, in retrospect, when he or she is old enough to say, will say, yeah, it was worth it, highly speculative, so

I think the notion that this kind of indirect reward is a benefit or will be perceived as a net benefit is speculative at best.

I think a modest honorarium for the parent and the child is a courtesy, a way of saying we appreciate what you are doing is a different issue. So, I think we are talking here about inducements which a competent adult can choose to make to expose himself or herself to major risks, but one which a young infant obviously can't.

[Slide.]

Similarly, the psychological benefits of altruism, and so on, while they can be appreciated by older children and certainly adolescents, they are obviously not susceptible to appreciation by infants, whether they would appreciate them in the future is highly speculative.

The balancing judgments by parents that it will be good for my child in the long run to be altruistic is speculative, but the main point is if families want to raise their children to be altruists, there are a hundred ways of doing it without enrolling them in a

non-therapeutic trial. That is, they can teach their children in all sorts of ways to be giving people, to volunteer, to work with church groups, to do free labor, shovel snow, rake the neighbor's leaves, and so on, and so forth. This is not an essential way for parents to impart values.

[Slide.]

Now, Question No. 1. Should a Phase I trial be considered beneficial? It has been pointed out by many that the likelihood of benefit in a Phase I trial is very low, generously, 5 to 10 percent of Phase I agents eventually are shown to be safe and effective and make their way to the marketplace. Some put this estimate a lot lower.

But the point I want to make is that many competent adults consider this a benefit. If you have a serious disease, particularly a fatal disease, such as cancer, for which there is no other effective treatment, even a very small chance at a benefit is a sufficient benefit to undergo considerable risks.

I would also point out that similar numbers may apply to standard treatments. that is, just the notion

that a treatment may have a very low chance of helping you is not restricted to experimentation. There are many standard therapies for cancer, intensive care patients, head-injured patients, and so on, in which there is a very low likelihood of benefit, but we consider parents to be appropriate proxies for deciding whether or not to expose their child to risks in exchange for those benefits.

A point, in conclusion, in my view, would be that whether the benefits are worth the burdens are questions about the validity of proxy consent, which other people will be talking about, but it is not a unique question to experimentation, nor is it unique to Phase I trials

[Slide.]

It has been pointed out that there are many qualifications about these sorts of benefits. They may be very low likelihood, they may be of short duration, they may be only palliative, and not curative, but these are qualitatively similar questions to those which arise in standard treatment. They are not unique to research.

These balancing judgments, as I said, I think

are questions about the validity of consent. So, I don't see a Phase I trial, even with its very limited prospect of benefit, being different from other judgments that parents are allowed to make. That doesn't mean they always make good judgments, they can make wrong judgment, but I don't see it as a different kind of issue.

[Slide.]

Now, placebos. First, a couple of definitional problems. Obviously, placebos can have real effects, psychologic and physiologic. I would just remind you that the Canadian growth hormone trial included a placebo arm, that is, placebo injection, and then a group that had no injections at all, and there was some effect on growth from those in the placebo injection growth, that is, injecting saline or whatever it was did produce some added growth compared to children who were receiving nothing all.

So, we always have to remember placebos can possibly have beneficial effects, as well as toxic effects, but in general, I think it is safe to assume that placebos are considered less likely to have a beneficial physiologic effect on the disease, so let's

assume that that is the case.

The second definitional problem is the definition of a placebo-controlled trial is a little fuzzy. If you do a trial in which Group A gets standard treatment plus an experimental treatment, and Group E just gets standard treatment, that morally would seem to me the same thing as a placebo-controlled trial.

That is, it is not the addition of the placebo that is problematic, it's the withholding of something that is thought possibly to be beneficial. It is the presence of nothing, not the presence of something.

[Slide.]

Well, this is the age-old question that Smithells, the great British trialist, raised, you know, why is it that I need permission to give a new drug to half my patients, but not to all of my patients.

In any randomized controlled trial, many children receive only the standard treatment, that is, all those untold numbers of children who aren't in the trial. To take a famous example of the low dose AZT trial in Africa and elsewhere, just making up these numbers, but approximately 5,000 children in--and this

was a drug given to mothers, but obviously, the intended beneficiaries of this were mainly the children, so I will all this a pediatric trial--5,000 or so got the low dose AZT, and 5,000 got placebo, which was for all of them standard treatment, that is, the treatment that they would have gotten had they not been in the trial.

In addition to the 5,000 who were exposed to placebo, there were a million or more who were also placebo treated, if you will, that is, who got only standard treatment.

So, if the objection, as Dr. Lurie and Dr. Angell suggested, is that some children were getting nothing, that is not just true of the children in the trial, it is true of many more children who were not in the trial, and that is true of any controlled trial. There will always be many, many children who are getting nothing, and we don't see that as a problem, that is, that all conceivable targets of the treatment are not receiving the experimental treatment.

[Slide.]

Can a placebo-controlled trial be considered as having the prospect of direct benefit, a question raised

by one of the Advisory Committee members earlier.

As Dr. Kauffman has pointed out, if innovative therapy is widespread, as it is, and if it is unproven and harmful, as it often is, the placebo arm may have the best outcome, it may be the best place to be.

Much has been made of sulfonamides and chloramphenicol. I just want to point out we could be here all day talking about dozens of examples of treatments that were done in an innovative way that have harmed hundreds of thousands and probably millions of children, used over decades, the number is legion.

I am just going to use one example, so I can refer to one with a couple points I want to make. When I was an intern and for a decade thereafter, every newborn with respiratory distress syndrome received what was called the usher regimen, a little card we carried in our pockets of administering concentrated bicarbonate based on the pH. These children were severely acidotic.

Dr. O'Dell, my colleague and mentor, screamed for years in the wilderness that this made no physiologic sense and that no clinical trial had ever been done. He developed an animal model that showed it did more harm

than good. I will come back to this in a minute, but the point is that being in a placebo-controlled trial, the placebo arm may be the place to be if you are getting any one of these treatments that turns out to be very harmful or at least harmful in a majority of cases.

There are, of course, as I have already mentioned, the indirect benefits of being in a placebo-controlled trial, the doctor having to be screened in some way for credentials, the need for a literature review, the peer review at multiple levels, and so on, and possibly a data monitoring board.

[Slide.]

Now, when should this assessment of benefit be made? Some people say, well, if you wind up in the placebo group, that is not so good. First, you can't make the assessment after the trial is over obviously. That is not fair playing to say after the trial, one group, the placebo group turned out to be not so well off. You don't know that. I mean that is a problem with any trial. When it's over, it was worse to be in one group than the other. So, you can't make this judgment after the trial is over.

Can you make it after somebody is assigned to the placebo group? Is there a way of knowing that you were in a placebo group, that your child was in the group saying I don't want to be in that group? Well, if the trial is truly an equipoise, as it should be for the IRB to approve it, that is not a fair question either. That is, you don't know at that point whether being in the placebo group is good or bad. As a practical matter, of course, people can't be allowed to opt out at that point.

That is, even if there is only a 50 percent chance of the experimental treatment being a benefit, even if you see that as the only benefit, even if you don't see being in the placebo group as being a benefit, which would be a mistake because it often is a benefit, even if you see the only benefit is as being in the so-called treatment group, if you have a disorder for which there is no effective treatment, a 50 percent chance at an effective treatment is better than no chance at all.

Again, this was one of the justifications for the low dose AZT trial. The choice there wasn't, for children, between low dose and high dose or 076 regimen.

The option facing children in Africa was no treatment, which was their background situation, and at least a 50 percent chance of some treatment was a benefit for being in that trial. It turned out to be a big benefit.

The Wisconsin Cystic Fibrosis Newborn Study is another example of this, but we don't have time to go into it.

[Slide.]

Well, as I said, there are three types of randomized trials in which these principles might be applied. The first would be one in which there is no known effective treatments, let's say for example, Jakob-Creutzfeldt disease becomes epidemic in the U.S., suppose a treatment--a diagnosis, first of all, is established, and suppose somebody is proposing a treatment. Nobody has any idea of any other way of helping these children. That would be one type of trial.

A second would be a trial in which there is widely used standard treatment that is unproven, such as bicarbonate for respiratory distress syndrome, and dozens of other historical examples.

And third would be a situation in which there is

a proven effective treatment and proposal to test a possibly better treatment. Let me just run quickly through each of t these.

[Slide.]

Let's take the CJD example, that is, a condition where there is no conceivable treatment, and let's say there were a way of diagnosing it. Would it be wrong to enroll a child in a placebo-controlled trial of this, would we say that the children who are in the placebo group are in a non-therapeutic situation?

Well, what is the alternative? The alternative would be to give it to everybody with the disease and hope everybody in the room appreciates that that is a bad idea and nothing that pediatricians or anybody else would want to get behind.

The no treatment arm, if there were a no treatment arm, would be more equivalent to placebo, it would be no different than standard care. The presumption that the treatment arm is better is false if we assume equipoise, and even only a 5 percent chance of success, there may be lots of toxicity and being in the placebo arm may be better.

So, being in the placebo arm is often better than innovative treatment. You don't know in a trial like this. That is why you are doing the trial.

[Slide.]

Situation No. 2. Suppose there is a situation for which there is effective treatment, is known--well, this is actually a variation on No. 1, I apologize.

Supposed effective treatment is known, but is unavailable, such as the low dose AZT trial in Rwanda, for example, or suppose somebody were proposing a dietary treatment of renal failure in Rwanda where dialysis is completely unavailable.

A placebo group in this situation is not being deprived of anything to which they were entitled or to which they would otherwise have access. That is, they are no worse off, there is no harm of being in a placebo group in this trial. As I pointed out earlier, all those not in the study are also being denied treatment. So, the criticism that being in a placebo group could be equally applied to all the millions of children who are not in the study.

[Slide.]

A question was raised this morning about harmful placebos, such as injections in the growth hormone trial or sham surgery, a more serious concern. I think the presence of possible harm in the placebo or likely harm, such as the discomfort of repeated injections, raises the stakes for good design, but doesn't end the moral propriety or terminate the discussion of the propriety of the trial.

I mean the growth hormone trials are problematic for me because they had the wrong endpoint, not because half the children were getting placebo injections. That is, you still may be better off in the placebo injection group. You just don't know at the beginning.

[Slide.]

I will skip this because I have gone through it already.

[Slide.]

The second type of trial I referred to is in which there is standard, but unproven treatment, of which there are, as I said, dozens of examples, such a bicarbonate for RDS, the use of the new PKU diet in the 1960's, and so on, which ultimately turned out to harm

great numbers of children, who did not have PKU.

The problem with not having a placebo group is a design problem, that is, suppose in the bicarbonate situation, there had been a trial in which half the children got bicarbonate and half got experimental treatment, and they both wound up with the same survival rate. The problem with not having a placebo group is that you have no idea what the background rate of harm and benefit is, that is, what the outcome is.

This is the central problem of not having a placebo-controlled group is that when the trial is done, you have no idea whether both agents were effective or neither was effective. So, morally, you are exposing children in a trial of poor design in which they are being exposed to some risk with no possible benefit or at least no way of knowing whether they were benefited or not.

[Slide.]

The last example. I just want to point out that even when there is proven effective treatment, it wouldn't be the case such as bacterial meningitis, let's say, or ALL with an 80 percent cure rate, it wouldn't be

the case that a placebo-controlled trial is de facto immoral.

It is obviously wrong to withhold proven effective available treatment for a child with a life-threatening disease, such as this, but you can, first of all, it should go without saying you can add an experimental drug to the standard regimen versus placebo as long as everyone is getting standard treatment, but I just want to point out that competent adults sometimes choose to forego proven treatment because of concerns about risks or other kinds of burdens. It is not inconceivable that a thoughtful parent might do the same for their child.

I would just give one specific example that we may talk about later. ALL has 80 percent cure rate with a certain high level of toxicity. There is some interest now in exploring treatment regimens which might be less toxic, that is, in having a treatment group that gets something less than present standard treatment, and in which the control group would get standard treatment or a standard treatment plus placebo.

I don't think we can presume a priori that

withholding standard treatment is wrong. Many adults make this decision, many thoughtful parents may make it. It is a question about the validity of proxy consent, but it is not de facto wrong to withhold standard treatment.

[Slide.]

The last slide, I think is a summing up slide. Benefits, as I said, may include not just direct medical benefits, but the indirect benefits of being in a trial, access to treatment where none was available.

The money and rewards and the psychological benefits, I think should have relatively no relevance for small children, infants, in particular. Being in a placebo-controlled trial may be a benefit. The placebo arm may have a better outcome, and there are the indirect benefits.

[Slide.]

The slide. Even remote benefits and high burden, which would be true of most Phase I trials, may be justified in some cases, and a disinterested advocate for the child would not necessarily reject all such proposals.

Analysis. So, I don't think this can be reduced

to an algorithm. I am not optimistic that the FDA can create algorithms on what may or may not be approvable by an IRB. An analysis of each case depends on the validity of standard treatment, on the seriousness of the disease, the burden of the intervention, and some fundamental value questions about whether the risks are worth the possible benefits.

Thank you.

DR. CHESNEY: Thank you, Dr. Fost.

We could take one or two questions. Yes, Dr. Kauffman.

DR. KAUFFMAN: One of the problems that we are currently confronted with is--and this is in the context currently of new drugs for hypertension in children or behavioral psychiatric conditions--the proposed protocols are asking us to subject the child to a prolonged washout period with no treatment prior to entering the study, and this is a major issue for us. We don't know how to deal with it.

DR. FOST: These are children with hypertension you are talking about.

DR. KAUFFMAN: Well, they are children, yes.

They would be children who are receiving some sort of medication for hypertension or children with, let's say, ADHD, who are on a stimulant for ADHD, and to enter the protocol, they have to undergo three or four weeks of washout with no drug to qualify.

DR. FOST: Well, my reaction would be, as I said, first of all, an assessment by the IRB and the parents and others as to whether there was a benefit, potential benefit to the child of being in the trial overall, of which there would some risks, at which the washout period would involve some risk.

Washout periods, if the child has a mild disorder like mild hypertension, ADD, not life-threatening, and so on, the risk of being off medicine, off medication completely for a period of weeks may not be a very great burden. It may be worth it to be in that trial for all the reasons that I mentioned.

So, I wouldn't exclude washouts as morally indefensible. In some situations, a disinterested advocate for the child might think it is well worth the child to be in the trial, all things considered.

DR. KAUFFMAN: How about an antidepressant?

DR. FOST: Again, it would depend on what the implications of being off the antidepressant were for three or four weeks. We all know of the UCLA case in which-- well, that was a schizophrenic--but in which somebody killed himself while on a washout thing.

If somebody has a severe incapacitating disease where there is some serious risk of being off medication, that would create a very difficult standard to overcome, but not everyone who is depressed is going to be profoundly disabled from being off their medication for a period of weeks. That has to be balanced against what the benefits for them might be of being in the trial.

DR. CHESNEY: Dr. Walter.

DR. WALTERS: Norm, thank you very much. Do you think that there is no role at all for historical controls in clinical trials, that is, are historical controls no controls at all, number one? Second, what about using the results of placebo-controlled groups from earlier studies as a kind of baseline for new studies that don't have a placebo group?

DR. FOST: I wouldn't say no basis. Obviously, a randomized controlled trial is not the only way of

gaining knowledge, and God knows, from epidemiology, that we learn a lot by case controlled studies, and so on, using retrospective data.

I would just say, though, in an intervention trial, it is really hazardous. There are just so many examples in which things change that you are not aware of, the so-called Stallman effect in pediatrics, that is, different centers have different levels of intensity of caring for children. It may be the nurses that are making a difference. You just don't know what the variables are that may have affected the outcome.

You also don't know, Leroy, about the variability of disease, that is, the historical control that you are using, or the placebo group from the previous thing, it may be a disease in a village or in a county or in an ethnic group, that has a very different variability, a very different outcome than the group that you are studying.

I would just point out that the transmission risk of HIV in New York State varied from 5 percent in some parts of New York State to 40 percent in some parts in the South Bronx. So, relying on some previous

estimate of what the transmission rate is from some previous study, you have no idea whether the group that you are looking at now has that.

So, all these familiar problems, I think argue strongly in favor of presuming that a prospective randomized trial for an intervention study should be the preferred way to go.

DR. CHESNEY: One quick question and then we have to move on.

DR. WARD: For the FDA, it would be interesting for them to answer whether if the active control is an unlabeled and currently unapproved treatment for pediatrics, whether that is an acceptable control.

DR. MURPHY: Thank you. Good question. I think that there is no absolute answer. It is unlabeled, so, yes, it is not what we would always--would not accept in adults, however, there are situations in which we have tremendous experience and data in which it would be wrong to say that that experience doesn't count, and so how you design the trial may depend on what other data you have at that time.

DR. CHESNEY: Our next speaker is Dr. Wilfond

from the National Institutes of Health, who will speak about risk in pediatric research.

Risk in Pediatric Research

DR. WILFOND: Thank you.

[Slide.]

As Norm talked about benefit, I am going to talk about risk, which is the second component of that risk-benefit equation that was alluded to earlier. I think in the end, I am going to be agreeing with a lot of Norm's conclusions, but I am going to get to them in a slightly different place.

I think the most important conclusion that he acknowledged that I would agree with is that all these issues need to be looked at in a very context-dependent fashion. It is very difficult to make broad statements about what things count as a benefit and what things count as a risk in a broad sense.

[Slide.]

I am going to actually disagree or at least suggest that we think about benefit and risk slightly differently than Norm did. I may be overstating his points, but this is the schematic for the categories of

risk and benefit as described by the regulations, and my point is not that I in any way take the regulations as being set in stone or we need to actually come up with important interpretations, but that this at least gives us some guidance to the fact that when we make decisions about the acceptability of research, we are somehow guided by these categories of risks and benefit.

I think there is a tendency to whenever looking at a particular study, if possible, try to think of that as in the category of benefit compared to no benefit because that allows a greater latitude for acceptability.

Similarly, if we are thinking about the risk issues, again, depending upon how we choose to label a particular activity and a particular set of risk, the more we can either move it to the left, the more likely it is going to be acceptable.

I think that there is a problem with trying to do that. The problem with that is that there tends to be, in general, an overestimation of benefits and underestimation of risks, and I think this may be challenged when we are trying to talk to patients and families about participation in research.

I think in the end, I come out in the same place about what studies are perhaps ethically appropriate, but I would be much more comfortable with acknowledging certain studies perhaps don't have a prospect of direct benefit and that certain studies, we might want to think of as being more an increase of minimal risk in terms of how we think about them.

[Slide.]

Again, we have already seen this definition of minimal risk. What I want to do is to focus briefly on the notion of magnitude and probability, the notion of daily life, and will talk about some things related to routine and psychological exams.

[Slide.]

One of the problems is again this notion of minimal risk is unclear. Some people have suggested that perhaps we are talking about issues of inconvenience or discomfort rather than long-term risk or harm.

There was a study almost 20 years ago now where a number of pediatricians were asked how they would describe the risk of tympanocentesis in their population, and what is interesting, I think is that there was a

fairly broad range of disagreement about how to label this.

I think the importance of this disagreement is that it may not be in and of itself terribly helpful to ascribe a particular category to a particular intervention unless we think more about the specific context and the benefits and the particular study that is involved.

I think what is important is to think that minimal risk at the very least is meant to be a threshold in which more careful scrutiny and evaluation by the IRB is important.

I think that the point made by Dr. Spielberg can't be overstated, which is the importance of minimizing risk, that depending upon the situation and how a study is done, there are many things that can be done in a particular study that actually reduces the risk dramatically compared to the same intervention being done in a different setting.

I think for that reason, the risk must be thought of as context-dependent, it must be thought about who the actual investigators are, what the actual setting

is. I think the description we heard from Dr. Kauffman of the research center that he has there is perhaps an example of where certain types of studies may be acceptable in that setting in contrast to other settings that may be less regulated.

[Slide.]

To finish up in terms of this notion of minimal risk, I want to borrow some thoughts from Loretta Kopelman actually, that is 1989, not '81, and this paper is actually included in your packet of readings.

She tried to ask the question about how we think about the notion of the risks ordinarily encountered in daily life, and she said there is at least three different possible ways of thinking about this.

We can think about all the risks that ordinary people encounter, we can think about the risks that all people ordinarily encounter, and we can think about the minimal risks that all people ordinarily encounter.

I think her point was when we think about all the risks that ordinary people encounter, that includes a wide range of things including riding in cars, football, bicycle riding in heavy traffic, and so that itself would

be an inadequate description of what we count as minimal risk.

Even for the notion of the risks that all people ordinarily encounter, there is still certain things that actually hold specific, although unlikely, but real risk of serious problems. That includes taking a bath.

The last one, of course, becomes a tautology because if you are trying to define minimal risk by defining it this way, it becomes difficult to have any clear idea what it means.

She also acknowledges that risk may vary with location, so if we think about the risks of daily life in Kosovo compared to the risks in South Dakota, they may be quite different, but I am not sure if that would be a justification for doing different types of research on children because their environment is otherwise hostile.

I think the other benchmark that is used is the notion of physical or routine physical or psychological exams. This might have some value in that it sort of points to our intuition that cardiac catheterizations are not, in general, the sort of thing that are usually involved in routine clinical care and perhaps ought to be

thought of as being something over minimal risk.

There are other risks that are routine that may actually have as much, if not more, significance than cardiac catheterization, and there is a wide range of risks that are involved in routine clinical care.

There are psychosocial risks that may be related to privacy and confidentiality and stigmatization that, in fact, may be very profound even those these occur routinely, but it is not clear that because they occur routinely, that that suddenly would suggest that they are minimal.

[Slide.]

I think the bottom line point of thinking about the notion of risk-benefit calculation, as it is described in the regulations for pediatric research, is to acknowledge a point that there is an intent for the regulations to be more restrictive than they are in adults, that there is meant to be some sort of truncated set of participation compared to what we otherwise would let adults participate in, and the challenge is to try to parse out exactly what that truncated set is.

I think that one of the examples I like to give

is that we really allow a greater latitude in choices for daily activities of parents, but we expect the parents might limit children's activities.

I want to use the example of bungee jumping and swimming because each of these has a certain amount of risks, but we could imagine parents of a six-year-old may look at bungee jumping and swimming quite differently.

To explain that, I want to borrow from what I think is one of the more interesting papers that I have read on this topic by Freedman, et al., that was also included in the packet from the Hasting Center about six years ago.

What they suggest is that when we think about risk and benefit, we really ought not to think of them separately, but we need to think of them in a combined fashion, and we need to think of this as being a normative assessment rather than just a quantitative assessment of magnitude and probability, and to ask the question whether the risks are worth the benefits.

The example that they give is of a child's first camping trip. When you think about it, there can be a wide range of risks of going on a camping trip. This is

not part of routine daily activity. It is not an experience the child has had before, but yet many parents make decisions at what point is developmentally appropriate for that person to go on their first camping trip.

They may look at issues about what is their supervision, where the camping trip is going to be held, and I think these things really perhaps may be a good analogy for how we think about pediatric research.

I am not saying that pediatric research is a walk in the park, but just that this notion of comparing them together may be very helpful. I think what the most important for me aspects of the Freedman paper was the metaphor they use of the scrupulous parent.

What they suggest in their paper is that perhaps what IRB's ought to be doing is tracking the decisions that a scrupulous parent would be making for their children. In other words, we could imagine a wide range of parents making a wide range of decisions, but a scrupulous parent, who is really concerned about the welfare of their child, and looking very critically at what is being involved, perhaps is what the IRB ought to

be doing.

I think that this metaphor is actually a very useful way of trying to overcome the challenges of labeling various research within the category of either minimal risk or benefit or no benefit.

[Slide.]

I think that in addition to risk, if you recall in the first slide, as you have heard from previous speakers, are additional considerations along with risk that need to be considered. I think thinking about them along with risk is actually very helpful.

The second criteria for studies that have greater than minimal risks, but without a prospect of direct benefit, include some notion of reasonably commensurate experiences.

I think the point of this is that having these sort of experiences may, from the perspective of the subject, be a way of the risk being either minimized or the discomfort being minimized.

In other words, a person who has had experience with a particular intervention may, by having had it before, have less anticipation, less fear, and maybe

also, secondly, be able to have a more genuine understanding of what it involves, and their assent will be based on perhaps a more clear understanding of what is going on.

So, I think that this notion of reasonably commensurate experience is very important as a way of at least allowing people to make assessments about risk.

This again also can't be overstated, the notion about the study involving vital knowledge about the subject's disorder or condition. I think the importance is that it emphasizes the value of the research in relationship to the risk.

I think where people get stuck is on this notion of subject's disorder or condition, because I think perhaps this is a line of the regulations that says perhaps we only can study subjects who have the disease in question rather than people who don't have the disease.

In the end, I think that this perhaps leads us to a somewhat problematic conclusion and that perhaps if we think of the subject's disorder as being some of the unique aspects of pediatric physiology, and think of

things that benefit children in general, that may be a more useful and robust way of thinking about it than just thinking about the disease itself.

What I am going to suggest is that we ought to think about these notions of commensurate experiences and vital knowledge in conjunction with the notion of risk.

To conclude, I have two slides to illustrate these points.

[Slide.]

I want to point out Phase I oncology research. We have heard a lot about that today and even though we are talking about healthy children, I think it is because Phase I oncology research is an example where we actually do involve children in fairly risky research.

The risks of Phase I oncology research might include the toxicity itself from the chemotherapy, the additional time may be spent in the hospital, potentially the foregoing of palliative care although clearly that doesn't have to be. There is no inherent reason that participating in a Phase I research would require that.

Another concern might be the false hopes that may be overblown depending upon how a project is

described. On the other hand, participating in Phase I research may actually increase access to palliative care particularly if it is occurring in a tertiary care setting where there is great attention to palliative care that may be integrated into the provision of those studies.

For many children, the hospital actually is a familiar environment and actually a place where they actually feel a fair amount of comfort. Again, this depends on the child, but it is meant to acknowledge some notion of benefits, and there may be the psychological benefit of participating.

Again, I tend to think of these as collateral benefits to distinguish them from the notion of direct benefits and in terms of my own set of calculations. While I think these are incredibly important, I would still tend to think of these as studies that don't provide a prospect of direct benefit.

I think, though, in terms of thinking about doing this research, which I am actually in favor of, I think that we have to think about again the notion of commensurate experiences. These are families that

actually have had chemotherapy before. They clearly have an idea of what they are getting into.

This is certainly very important research, and it is intuitively obvious that we would not think about giving highly toxic chemotherapeutic agents to otherwise healthy children, and I think that when we consider all these things together, I think it is at least possible that this would be an appropriate thing to do with these types of children even though, in fact, the actual risks appear in terms of toxicity would actually be less than healthy children because they probably, by not having cancer, by not having had chemotherapeutic agents, they are probably, if anything, less likely to experience the risks.

I wouldn't be suggesting we do this type of research on healthy children.

[Slide.]

So, let's get back to the notion of pharmacokinetic and safety studies in children. Again, we have to think about what the risks and discomforts of these are going to be for the children, and again, pay attention to trying to minimize those risks and

discomfort.

To the extent that this represents a commensurate experience really will depend upon the child. There may be some children where blood draws or whatever the intervention is, is something that they are familiar with and may be more willing to do, but that may be independent of the particular disease itself.

Again, I think that the last notion of the importance for the disorder really is what perhaps drives us, as was stated earlier, is the need for effective therapies, expectations of unique pediatric issues which if, as has been pointed out time and time again, the alternative of not doing studies and just doing this routinely may pose even greater risks to subjects.

I also think the questions about acceptability of alternatives, I now forget who said it, I think it might have been Dr. Spielberg, who mentioned the fact that there may be opportunities for doing pharmacokinetic studies along with studies of efficacy or perhaps in some circumstances even more rigorous postmarketing surveillance to try to detect problems with drugs.

As we know, there are many study drugs that go

through a fairly rigorous evaluation prior to approval, and it is only after a drug has been out for a number of years that later on low likelihood of risks become apparent.

I think in conclusion, I think when we think about doing these types of studies, selecting children who are already in the hospital, as Dr. Kodish will be talking about later, or who are healthy but have the condition, might influence these dimensions, but I want to actually suggest that in many circumstances, that we might be better off in these types of studies not doing studies on people who have the disease.

I think that a child who has asthma, for example, who already has a fair amount of need for medications and physician visits, may not be the ideal candidate for doing a pharmacokinetic study for an asthma drug that won't benefit them.

I think that I would be much more comfortable with a child and a parent who didn't have the disease, who for whatever reasons decided--I wouldn't say for whatever reasons--but decided to participate in an appropriately designed PK study perhaps being done at a

place like Dr. Kauffman's center, and I think that it is possible that a scrupulous parent might be more willing to allow their healthy children to participate if they thought that this was an appropriate experience for their child.

With that, I will end.

DR. CHESNEY: Thank you.

Any questions for Dr. Wilfond? Yes.

DR. NELSON: Ben, 46.406 requires that knowledge that might be of likely benefit for a child's condition be part of the approval process. My specific question is what I thought you implied is that simply being a child could be considered a condition for the purpose of approving research under the section, and I just wanted to ask you that to be clear I heard you correctly.

DR. WILFOND: Well, I don't have the actual text in front of me, but you are correct that I am sort of interpreting it in an unusual way. I think that the text specifically talks about vital knowledge about the subject's disorder or condition, but I think that the reason in many cases why we do pediatric research is because we want to gain specific knowledge about

pediatrics, and I think the motivation behind that portion of the regulations is that we want to avoid using children because of purposes of convenience, as Jeff described earlier, where because they happened to be there.

I think that if there is good argument for why this ought to be done in children, that we might ought to think of that in a favorable light. I take the regulations not as gospel, but as sort of a direction to our thinking.

DR. CHESNEY: I think we can take one more question, and then we will move on. Dr. Danford.

DR. DANFORD: It occurs to me that we might not really know some of the risks that we are subjecting our subjects to as we enroll them in these research projects, and that is obvious, I guess, because we are doing research to find those out maybe.

Must we make parents aware that we are dealing with guesswork when we assess the risks and they consider enrolling their children in these projects, and furthermore, do we need to let the parents know that there might be a conflict of interest in the people who

make the estimates of risk for them and that the investigators have a vested interest in the success of their research, and do ethicists or IRBs ever talk about full disclosure of that sort of a conflict?

DR. WILFOND: Regarding the second part of your question about conflict of interest, I think that that certainly is an issue. I think that that is an issue that is potentially inherent in all clinical care, that physicians have a wide range of self-interest that they need to manage when they interact with patients, and that is certainly true of researchers interacting with investigators.

I think one of the things that the IRB does is try to really look about how risk and benefit is described, and perhaps that is really where I am coming from in my initial slide, which is to really encourage a more clear and careful and accurate estimation of the risk and an accurate estimation of the benefits, because I think there is a tendency to increase one and decrease the other.

DR. CHESNEY: Thank you very much.

We will move on to Dr. Ellen Clayton from

Vanderbilt University, who will talk about assent, consent, and permission.

Assent/Consent/Permission

DR. CLAYTON: We were asked to give some background of information of things you might want to know, so you will know how to listen to what we are saying, so let me make a few disclosures about myself.

One is that I am general pediatrician and a law professor. I also was a research assistant to Jay Katz and his book on The Silent World of Doctor and Patient, and the final disclosure that I would make, as you will hear shortly, is that I am a physician mother who has enrolled her children in clinical trials.

[Slide.]

To begin this, in talking about informed consent, permission, and assent, I have to say just a few words about informed consent, not because it is generally applicable in trials with children, but because we need to understand the background.

One is that in terms of thinking about what is necessary to do informed consent, we need to assess the individual's decisional capacity, do they understand what

the options are, what the possible consequences may be, and do they have a set of values against which they can relate the consequences.

[Slide.]

There also has to be some sort of disclosure to the potential subject, and there have been endless amounts of work talking about what the standard of disclosure has to be. There has been a lot less research looking at how much subjects have to understand, but in any event, that is another issue, and then, finally, we also insist on some level of voluntariness.

[Slide.]

We spend some time thinking about how voluntary things really are, hopefully, beginning with an acknowledgment that nobody is a completely autonomous individual who is making decisions completely independent of everything else in their lives.

So, what we are really always on is some continuum between persuasion, manipulation, and coercion. I am finally going to say that we do recognize that some older adolescents are developmentally incapable of giving an ethically valid informed consent.

Now, whether that is legally valid or not, I think is a completely separate issue, and by and large, our law would say not, but nonetheless, clearly, there are some older adolescents who can do all these things that I talked about.

[Slide.]

Why do we care about informed consent? We care about it at least for two reasons. One is because we value, particularly in this society, the notion that people should be able to direct their own futures, I am the captain of my fate, and also because we view informed consent as a mechanism by which individuals can protect themselves from risks that they may incur in the research process.

How realistic the latter of these is, is I think a little bit hard to say, but I think the ongoing question, the one that I am going to come back to at the end, is whether, in fact, we can say that there are times when the good of obtaining generalizable knowledge may make it ethically permissible to do research even without consent.

This was a point raised earlier in the morning,

and it is one to which I will return later.

[Slide.]

But the fact is, in pediatrics, that informed consent isn't possible most of the time, and so what do we do? What we have done in the past is that we have looked for parental permission, we have talked about notions of child assent, and we have looked at other procedural safeguards, many of which we have already heard about, talking primarily about minimizing risk and looking at the possibility of benefit to the child.

[Slide.]

What I want to spend most of my time focusing on is this issue of assent. First of all, what is it? Is it just the little child saying yes, or does there have to be something more there? Do they have to have some understanding of what is going to happen to them, some idea about what the possible consequences may be?

They may or may not have a stable set of values, but do they at least have to have some idea of what is being talked about?

So, when we talk about that, that if it is more than just saying yes, then, we have to look at these

issues of does the child understand, does the child understand what the possible consequences are.

Now, as we look at this, we also have to ask why we care about whether the child assents or not, so we have to look at what those reasons are.

I am actually going to begin with one that is not on this slide here, but one which I think we need to acknowledge, which is one of the reasons we care about child assent is that it makes us feel better when we have it as investigators.

So, if a child has said yes, then, we can independently of the moral value of their particular decision, it makes us feel less bad.

But there are actually two other reasons why we think about child assent. One is because we want to honor their developing decisionmaking capacity. It is clear that children do not go from being an absolute tabula rasa to a complete, fully-fledged decisionmaker at the age of 18. Actually, it is unclear when they become fully-fledged decisionmakers, and 18 may be a particularly bad time, but nonetheless, it is not just an all or none phenomenon.

In fact, those of us who are parents realize that children get better about making decisions as they get older, and that if they didn't have opportunities to make more and more decisions as they get older, it is for sure that when they get to be 18 or whatever, that they will be terrible decisionmakers.

So, there is a really utilitarian view in wanting to promote their decisionmaking.

The other argument that is commonly made is that we also want to seek their assent in order to demonstrate respect for them as human beings, to identify that we recognize that they are not just the pawns of their parents, but they, in fact, are individual little human beings who have wants and desires and needs.

Now, why do I spend a little time talking about why we care about this?

[Slide.]

Because it depends on what weight you give to these two factors what you do about assent. Bill Bartholme, in the materials that you have here, really focuses on the need to respect children, and he talks about in his own work his recognition that what children

want more than anything else is for someone to respect them.

So, as a result of that, he would really pay enormous attention to objection and really much less attention to notions of the desire to enhance or encourage the growing decisionmaking of the child.

The other view that is evidenced in many of the materials that you were given today is that if you want to pay some attention to their decisionmaking capacity, then, the weight that you give to the assent depends on what kind of decisionmaker they are.

The decision of a three-year-old to agree to participating in a particular trial in order to get a piece of candy is worth less weight than the view of a 14-year-old who wants to participate in a study because they think it might benefit other children in the future, because they can actually assess what the risks and benefits to them are, because they can see the value of altruism, because they can see the value of scientific knowledge.

If, in fact, your focus is on the nature of the decisionmaking process, then, it becomes clear that the

weight that you give to the child's assent varies and increases largely with age, but also with the child's developmental experience.

[Slide.]

But I think what is really the harder issue here is not what you do when you have a child who assents, but what you do when you have a child who objects. I think that this is really in many ways the much harder question for this reason.

First of all, let's look at the older child. When you talk about the 14-year-old child who is given the opportunity, for example, to do the taste test study that is the first one before us, you might, in fact, think that an older child who objects to this is, in fact, kind of a bad kid, and, in fact, that one might say that the parent in that setting or the investigator in that setting might say, gee, this is really pretty benign for you, you know, why are you being this way, I mean are you just being a jerk or what is going on, so, because there is more opportunity to talk about what is going on.

What I really want to talk about is the younger child because it is pretty clear that unless you actually

look at the extreme, I think what I would call the Bartholme view, in fact, we realize that little kids can't assent, and so really all we have to look at is whether someone has managed to coax them into not objecting or what we do if they do object.

Here is the story that I will begin to tell, that I am going to expand on when I get to the role of parental permission. Since I am at Vanderbilt and because we are immunization heaven, both of my children have been in nasal flu vaccine studies, and what these involve is that the kids get the flu vaccine in their nose, they get a blood draw, and then sometime later they get another blood draw, but the thing that they hate is not getting their blood drawn, I mean they hate that, all kids do, but what they really hate is that if they get a cold, they have to get their nose washed out.

I can tell you that both my kids, when they were going through these studies, you know, got to the point where they would come to the clinic where I work, and they would just say, "No nose wash." I mean they hated it. Even if they weren't coming for the flu study, they just knew that if they came to the Peds Department, that

it might mean nose wash, and they hated it.

So, this was really quite onerous from their perspective.

Now, what should I or what should the investigators have done in that setting? Certainly looking at a Bartholme viewer, even looking at NBAC's recent report on decisionally impaired subjects, what those would say is that in the event of an objection, you stop right then. That is the end of the discussion.

So, I think the question that we are left with here is, is that, in fact, a reasonable response, and is that, in fact, what we really ought to do.

So, I would just lay this out there, that I think the real issue that we are required to pay attention to here is do we immediately stop when the child objects, realizing that the child may object for really trivial reasons or really not, or because, in fact, the child views the intervention as entirely noxious. Having had nose washes myself, in fact, I can tell you that they are really obnoxious to have.

So, that, I think, is what some of the major issues with child assent are.

[Slide.]

Now, the other option is if we are not going to pay attention to assent, or in addition to paying attention to assent, how do we think about parental permission? Now, here, I think it is incredibly important that we avoid the language of consent, and that we be serious about sticking to the notion of permission because this is really, honest to goodness, proxy decisionmaking.

I want to lay out some of the arguments that I cribbed from Dan Brock, to lay out some of the arguments that are being made about why it is a good idea to have parents be the surrogate decisionmakers.

The arguments are that parents are going to be more likely to consider the child's interests, that they bear the consequences most directly, that parents have the responsibility for socializing their children not to be hoodlums, but to be, in fact, altruistic good people, increasing notions particularly in my part of the country about family privacy, which is don't tell me what to do with my kid, I am the one who is going to raise him, and you have nothing to say about it, and notions that the

child would want their parent to decide these things given that they can't decide them themselves.

Now, I mention all of these to say that we look at them, but, in fact, there is little empirical evidence to say that any of them are really true, or that they are completely compelling, and to say that, in fact, there are other things going on.

Certainly I use the story of the child flu vaccine to bear this out. I mean one of the nice things about the child flu vaccine is they had a 90 percent chance of getting the flu vaccine, which was a good thing, but clearly, if I were just focused on my children's interests, they would much rather not have been in that study than been in it.

I also did tell them that they were getting some money, and it would go in their college fund, and they could go to Yale when they grew up, and this was good thing, and, you know, all that stuff.

Certainly it is true that I bore the consequences most directly. All those other things are true, but to say that somehow I was a great decisionmaker in that particular setting fails to acknowledge the fact

that I love vaccines and I love research, and I think this is good stuff.

So, as we look at this notion about what the role of parental permission is, we need to recognize that it is not a sufficient proxy for the child and that we cannot say that just because there is parental permission, that all the interests and concerns of the child have been met, and so that we are completely out of the woods because we have permission.

[Slide.]

So, I think that the real issue that we are forced to deal with here is, is it ever permissible to do research without assent and/or parental permission. I think the problem of objection if one that we have not fully addressed yet.

The other question that we have to deal with in terms of asking for assent is that certainly one of the primary rules of parenthood and one of the primary rules that I was taught as a resident--and Norm Fost was my teacher, so that is probably another reason I am here--is that it is a bad thing to ask children for their permission if you are not going to do what they say.

If you are going to do it regardless, then, don't ask them. The point that I have already raised here, there are some real questions about the sufficiency of parental permission, and the fact that both parents and investigators have conflicts of interest.

So, I guess my bottom line here is that I do believe that there are going to be situations in which you cannot get assent and which parental permission is actually not going to be sufficient to provide protection.

So, here is my final comment, and then I will open this up for questions, which is that I think really what we are left with here at the end of the day, when we talk about assent and permission, is that we do have to face up to the issue and say is the social good of getting the information that we want sufficient to permit certain kinds of research even without assent and even in the face of parental permission, and that I think, as I read through the materials, that we do not have not an adequate consideration of the utility argument that Jeff so well laid out earlier today.

I think as we go forward with this, if we do

give weight to the utility argument, that we need to be mindful of our tendency both to overestimate benefits and underestimate risks, and be mindful of the history that we certainly have, that children have routinely and systematically been abused in the context of research in the past.

End of comments.

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

Questions for Ellen? Yes, Dr. Nelson.

DR. NELSON: You failed to mention whether your children got a nose wash.

DR. CLAYTON: Oh, they got several.

DR. NELSON: Over their objection?

DR. CLAYTON: Oh, yeah.

DR. FOST: But, Ellen, that was a therapeutic trial, was it not?

DR. CLAYTON: Well, you know, they had a 90 percent chance of having gotten the vaccine, and 10 percent not, and, you know, flu is around, but, you know, the fact of the matter is they were healthy kids. One of them had asthma, so it was even more therapeutic for him, but the other one wasn't, and they just--you know, and as

Bill points out, I mean little kids hate that stuff.

So, yeah, I mean there was a potential benefit there, but if we are serious, looking at what Bill would say, then, one would have said that perhaps I should stop.

DR. CHESNEY: Dr. Fost.

DR. FOST: Well, I am not sure. Bill has passed away, unfortunately, who is responsible for much of what we are talking about today, but I am not sure what Bill would have said. He surely would be opposed to a completely non-therapeutic study of almost any risk, but given that situation where one of your children had a chronic illness and stood to benefit from access, a 90 percent chance of getting access to an agent that he otherwise wouldn't have been able to get access to, I assume--

DR. CLAYTON: Well, he could have gotten flu shots.

DR. FOST: Right, but this was possibly better.

DR. CLAYTON: Yeah, well, I mean--

DR. FOST: I don't know that that is any different than the judgment that you would have made

about giving him a standard flu shot. He wouldn't have wanted that either.

DR. CLAYTON: Well, he wouldn't have gotten it either. But I am just saying that depending on how one looks at this, I mean if one were to take the NBAC position on decisionally impaired subjects, and to apply it absolutely to kids, then, we absolutely should have stopped. I am not sure that that is a position that we can tolerate.

DR. CHESNEY: Dr. Gorman.

DR. GORMAN: Do you feel that either IRBs or principal investigators or sponsoring organizations have a responsibility to look at studies that either have low enrollment meaning many people are offered but few choose to do the protocol, or high premature terminations to see whether or informed consent was truly informed?

DR. CLAYTON: I think that would be a really good idea, and the reason that I say that is that often when people either decline to participate or when they drop out early, it is because the study is considerably more onerous than people thought going in, and they may, in fact, have known about it beforehand, but nonetheless,

failed to have sufficient appreciation of what was really at stake.

DR. GORMAN: So, as we, as clinical researchers, wrestle with informed consent, this perhaps should be yet another outcome measure?

DR. CLAYTON: Well, I have to say that in some of the work that I do, I actually go back and do retrospective studies about what people--first of all, what they got out of the consent document, and whether they actually understood what they were getting into, and what they have thought about being in the study after the fact.

Now, I do primarily research with adults, but I think that Dr. Kauffman's study, which showed that, in fact, you know, if you do it right, the majority of kids--I mean kids actually can be altruistic. It is one of the amazing things about kids. So, I am quite clear that there are a lot of things that they can believe are a good thing to do, but I think we won't know that unless we ask them.

DR. MURPHY: Ellen, I have one last question. Did your children express their great joy in being

altruistic at getting nasal washes ever?

DR. CLAYTON: I haven't reminded them now that they are old enough to give me a comment about that. So, no, I mean--

DR. MURPHY: I would like to add a different perspective to this even. I think what this discussion also brings forth is not only the ethical issue, but that the drive that the whole area of performing clinical trials will bring in, not only new endpoints, but also in making things less noxious for children, and having done flu diagnostic work, we developed the cool approach to this, which is the snort and blow snort approach, which one develops new techniques for some of these also.

DR. CHESNEY: Thank you, Dianne.

Our next speaker is Jonathan Rackoff from the National Institutes of Health. He is going to talk about compensation.

Compensation

MR. RACKOFF: Thank you. In the vein of disclosure, I should say that my research for the last four to five months has been on a number of issues in compensation, particularly those in pediatric research,

so that accounts for why I have tapped to give this talk.

[Slide.]

As we conduct more pediatric research and the pressure to recruit child subjects, and where they need to pay for their participation is likely to increase, you may be surprised how common payment has already become.

Paying for children's participation is an element of 25 percent of all pediatric and neonatology trials, at least that many advertise for compensation, and this data is from CenterWatch, a prominent clinical trials listing service.

When amounts are quoted, they typically range between $200 and $400, and there is anecdotal evidence for payments that even exceed $1,000. As the practice becomes more and more prevalent, we have to ask whether or not it is appropriate.

[Slide.]

We can't expect much guidance from the bioethics literature unfortunately. To a large extent, it has been silent on the question of whether or not children or their parents should be paid for their participation of children in research, but the American Academy of

Pediatrics does have a policy statement on point. Specifically, it recommends that if parents are paid, they be given only a token of appreciation. I guess what is meant here is a relatively small amount of money. And if children are paid, the AAP recommends that the fact of payment actually be withheld from them until the study's completion, hopefully, to ensure that payment is not part of the reason that a child volunteers or is volunteered for a study.

[Slide.]

There are a variety of different concerns that have plagued people who have thought about this, about the issue of payment in general, payment to anyone of any age. There are four main concerns. The first is that payment may represent undue inducement. This is essentially the view that subjects become so captivated by payment that they ignore other factors relevant to their decision to participate in research.

The second worry is that payment may disproportionately attract the economically disadvantaged to research. This is a traditional justice worry about the poor bearing an undue burden.

[Slide.]

The third concern is that subjects who are paid may not share the goals of research. This is the altruistic motive, the worry that they will do it for the money.

Finally, there is a concern that paying subjects represents commodification, that the relationship between the subject and the investigator and the subjects' participation itself may take on an inappropriate economic character or dimension.

[Slide.]

Over time people have attempted to resolve these worries in a variety of different ways, the most prominent of which has been focusing attention on how much subjects are paid with the idea being that if you can reduce the amount that they are paid, then, these worries will somehow disappear, but unfortunately, all four issues remain contentious and adults continue to be paid.

In order to evaluate whether or not it is appropriate to pay children per se, or at least to pay for children's participation, it is necessary that we

look at concerns that are unique to payment in the pediatric context.

[Slide.]

There are three broad areas of concern when we think about the ethics of paying children or paying for children's participation.

The first is a concern about exploitation, that parents will for self-interested reasons, namely, to get the money, may enroll their children in risky research, and that this will represent exploitation.

The second concern is that parents, in attempting to make good research decisions on behalf of their children, their judgment will be distorted and that they will get judgments of best interests wrong.

Finally, there is a concern about compromised assent, as Dr. Clayton touched on. Children may not consider all the factors that are relevant to their agreement to participate.

[Slide.]

These three concerns can best be understood when viewed through the lens of best interests, that is, the standard with which parents it is generally agreed should

make research decisions and clinical decisions for their children. In clinical research, parents in most cases should give permission for studies that serve their child's best interests, and there may be exceptions for nasal washes and the like.

Best interest definitely requires a judgment call, and it can be hard to know what is best for a child, and as a result, parents have substantial discretion in deciding or identifying what their children's welfare interests call for. But this discretion is not unlimited.

[Slide.]

Sometimes parents' decisions clearly violate their obligations to their children. In extreme cases, the courts will intervene.

This case is from a Jehovah's Witness case from 1944, in which the court wrote that, "Parents may be free to become martyrs themselves, but it does not follow they are free in identical circumstances, to make martyrs of their children." It is reinforcing the idea that best interests ought to be at least the first standard.

[Slide.]

Looking at these three concerns in greater depth, and through the lens of best interest, it becomes clear that exploitation occurs when parents disregard the best interest of their children, but this is not sufficient in order for exploitation to occur of parents exploiting their children.

There need to be three elements present. This is adapted from Wertheimer's book on Exploitation.

The first is that parents must take advantage of their children's vulnerability. Here, we mean that children rely on parents to make good decisions for them, and if parents deviate from that standard, make decisions for reasons other than their children's welfare, this violated children's vulnerability.

The second is that children are exposed to burdens and risks of harm while they are in research. It would seem kind of strange to say that a child was exploited if there was no conceivable way that the child could object, although some would say that that is exploitation nonetheless.

Finally, that parents accrue some kind of benefit. Here, the idea would be that they get the

indirect benefit of payment to the children.

[Slide.]

One has to ask how likely is it that parents, for the average of $200 to $400, are really going to exploit their children, enroll their children in research that is not in their interests.

The answer to this is unknown, but it is a definite possibility. Parents can easily access the earnings of their minor children and, as a result, they can be tempted by them, even $200, and this is particularly concerning when you are dealing with parents that have less money.

There are precedents for parents not always acting in the best interests of their children. Child abuse and neglect are prevalent, and this is good evidence for that.

[Slide.]

The second major area of concern with payment for children is that payment may skew parents' judgments about what is in their child's best interests, and this can happen in essentially two ways:

Payment may distract parents from other

considerations that might be relevant to the determination of their children's best interests, and it may also cause them to overvalue payment relative to any disadvantages that the parent is using payment to offset the disadvantages of research in determining whether or not that study has a favorable balance of risk to benefit for their particular child.

[Slide.]

Finally, the third major area of concern is that payment compromises children's assent to participate in research.

Now, adult informed consent, as we have heard, can cause a number of things. The first is decisional capacity, it also requires disclosure. It requires disclosure of the risks of research and the other burdens that might be involved, comprehension of these risks, and that the agreement to participate has to be above or it has to be voluntary, and all these qualities have to be above a certain threshold.

Due to obvious developmental difficulties, children's assent won't meet the threshold for consent in adults, and exactly what the threshold for children

having these four qualities has to be is unclear, but the worry is that since children typically have very little money that the control, pediatric payment might always represent undue inducement, it might always push children below the threshold for valid assent.

[Slide.]

Now, exploitation and distorted judgments, they sound very scary, but how great is the harm? This is debatable, but I and others in my group agree that the harm generally varies with the risk that a child is exposed to in the course of involvement in research, and this is very important because in federally-funded research, the Common Rule limits children's allowable exposure to risk, as we have heard.

[Slide.]

Specifically, research should not be approved that presents children with greater than a minor increment over minimal risk, without a prospect for direct benefit. These terms are difficult and open to interpretation, but the danger that pediatric payment poses to children is limited to the extent that IRBs are able to properly enforce the required risk categories.

[Slide.]

Now, for the most part, as far as I am concerned, in federally-funded research, these risk categories alleviate much of the concern. Payment of children seems to be, while still perhaps problematic, not obviously unethical or inherently unethical, but if you are not persuaded by that, there are other things we can do.

The AAP has recommended that, as I mentioned before, information about payment be withheld from children until the conclusion of the study, and this definitely eliminates any risk of compromised assent, but there still may be problems even with well-intentioned deception, this raises ethical concerns, this deferred disclosure.

Since there are other protections available, deferred disclosure probably is not warranted. Again, this is open for debate, but this is our view.

[Slide.]

There are four--and there may be more--but we identified four safeguards that will make payment of children even less problematic.

The first is to extend the risk limits that are inherent in the Common Rule, the subpart on kids, to all privately funded studies. The worries about exploitation and distorted judgment become very troubling indeed in studies that don't have those protections.

In all studies, the ways and the amount children are paid can be adjusted. We can use deferred or non-monetary types of payment. This would be savings bonds, college bonds, or gift certificates, and children can be paid less instead of more. It is certainly very difficult to identify exactly how much they should be paid. It depends on some sort of model for why they are paid beyond the augmentation or recruitment, but even a ceiling might be established, say, $300, and that is open for debate.

Third, the amounts paid to parents could be limited to reimbursement for incurred expenses. Both 2 and 3 here reduce the temptation that parents will face to give consent or give permission for children to be in studies for the money, and it may be possible or acceptable to pay them a little bit more than that, some minor increase over that reimbursement level, but

certainly we don't want to give parents any incentive to enroll their children.

[Slide.]

Finally, we could provide explicit guidance to parents in the parental permission form about the role that payment ought to play. This is a rich area. There are a lot of things that could be suggested, but I have provided some possible language.

"Payment is offered in appreciation for your child's participation in this study. We do not intend it to compensate for risk. In your judgment, participation in this study should be in your child's best interest."

Maybe it would be appropriate to provide some comment about exceptions to that here.

"However, you are free to waive payment in deciding if this study offers your child a favorable balance of risk and benefit." Here, we are allowing parents, since IRBs presumably haven't factored this in, to view payment as an indirect benefit that offsets the disadvantages of research.

To sum up, taken together, the risks that payment presents to children probably aren't sufficient

to call the practice inherently unethical or unethical in principle, but the protections that we institute and how we pay will be crucial to the ethics.

That's it.

DR. CHESNEY: Thank you.

Any questions? Yes, Dr. Edwards.

DR. EDWARDS: For someone who has been washing those noses at Vanderbilt for nearly 20 years, I have a couple of points. First of all, I think that social situations have changed and that there are more mothers and fathers both working, so I think that the necessity for some compensation to the families because of missing work or other day care kinds of situations are more of an economic reality now than they were a number of years ago.

I guess the second point that I actually would like you to comment on is that sometimes when consent is given with assent of the patient, particularly if the patient will be coming at multiple visits and will get some sort of compensation, you know, $10 for each interaction, nose wash or what, that the children or the adolescents are very excited when they come in and will

get some sort of compensation, but then the next visit it has become very clear that the child or the adolescent never sees that money, that, well, mom, you used that to buy the groceries, or you used that to buy whatever you wanted, and sometimes I certainly don't want to be a police person for those interactions, but does that change the consent when you realize that something that the assent was given for something positive has been taken away, does one need to reevaluate whether that is an acceptable risk-benefit ratio?

MR. RACKOFF: Two very good points. I will take the first one first. The issue of paying for time or for opportunity costs really is a thorny issue, because you are going to get into issues of equal treatment, because obviously, the mother, who is an investment banker, is going to incur a much greater opportunity cost than the mother who is working in the local diner, but to the extent that you have really economically disadvantaged families that need to have some kind of compensation to keep them going, well, certainly there is going to be a stronger tendency to provide that on the part of the investigators, otherwise, they are not going to

participate in the study, so it is something we have to look at.

As far as the issue about assent and parents taking the money, I am not really sure what to say. It is going to be a continuing problem. One of the possible solutions might be to attempt to point out to parents from the get-go that the benefit of payment, the benefit that it represents is intended to accrue to the child.

There may very well be well-intentioned parents who don't realize that, you know, this money is being given to Billy and it is totally appropriate for Billy to give it to me, and if we let them know that that is not appropriate, maybe that will offset some of the concern.

DR. CHESNEY: Dr. Gorman.

DR. GORMAN: The concept of a cap on payment for clinical studies is troubling due to the wide variation of the risks or benefits for children in those studies.

Most of the people in this room, I suspect, are reimbursed or compensated for both the complexity of their jobs and the risks they take. We have scales of reasonable and customary fees that we are paid for certain services.

Would that be an ethically acceptable model if someone could come up with that value, how much is a visit worth for a patient, or a bone marrow, or a nasal wash, or I am thinking of all the other terrible things I have approved in my studies, in my IRB studies, endoscopy, is there a construct that you would find ethically acceptable that would allow some expert body to put a value on those?

MR. RACKOFF: I think the answer to that question would be certainly yes in adults, in fact, many have proposed that adults be--or someone proposed that adults be paid for time punctuated with additional funds for onerous procedures.

The issues in children will be the same, though. I mean if a child has to undergo a particularly uncomfortable procedure and is going to be compensated at a rate that would seem appropriate, that might be a good deal of money, and we are going to need to weigh the concern about exploitation against the worry that that onerous experience won't be adequately compensated.

DR. CHESNEY: One more question.

DR. FINK: You made the comment I think it's a

widely perceived perception, and I am concerned about payment being coercive, that it would attract the disadvantaged and the economically poor and the minorities, and is there really any data, because my experience has been I get--my problem is recruiting the inner city patients even though I am in an inner city hospital--and I get a much larger suburban population participating in clinical research where the payment is less important.

I am not really sure there is truth to the statement that payment will unduly influence minorities or the economically disadvantaged. Is there any data to really back up that comment?

MR. RACKOFF: I am not sure that there is good data to back up the concern that payment would unduly induce anyone. On some level, it just makes sense, if you make minimum wage and someone is offering your child $1,000 for four weeks or procedures, that that would serve to provide a big incentive to agree, but I don't know of any good studies on that.

DR. CHESNEY: Thank you very much. The good news it that they are working on supply air conditioning

to the room. Our next speaker is Dr. Eric Kodish from Case Western Reserve, and he will talk to us finally about non-beneficial research in relatively sick children.

Subject Selection, Ethics and Pediatric Research

DR. KODISH: Thank you.

[Slide.]

My initial perspective to share with you is that of a clinician who cares for children with cancer, and also the perspective of being the last in a series of I think very interesting talks, so I am going to try to be brief because I want us to be able to eat lunch and fuel our brains for what I think is going to be an important discussion this afternoon.

I have decided to really talk about subject selection and focus on the question of having made the decision that we are going to do research without the prospect of direct benefit, is it morally better to do that research in sick children or in well children.

I think there are a lot of interesting questions about the former question that I mentioned, but the assumption that you all need to have for this talk is

that we have answered that already, we are going to proceed with that kind of research.

To lay the foundation for my discussion of this sick children versus well children subject selection, I am going to talk a little bit about Phase I oncology trials to begin with.

[Slide.]

I hope that this will provide some context. I think the term used in the past for Phase I oncology research both in children and adults that has been important is "therapeutic intent." I would focus on the word "intent" here.

The data demonstrate that there is an objective response rate of between 5 and 7 1/2 percent for children that are in Phase I trials. A response rate includes complete response meaning that the tumor has gone away, and a partial response meaning that the tumor has shrunk to some degree.

I would ask the question that if that is too low of a threshold to call it research with the prospect of direct benefit, then, what number would one give? Would it be 10 percent? Would it be 30 percent? Would it be

50 percent? One gets into a numbers game here.

I think the term "therapeutic intent" is important because it demonstrates the fact that it is possible to have more than one intent when one does something. The example I like to use is that I like to mow my lawn. I like to do that because it gets me away from my kids when they are nagging me, but I also like to get outside and be in the fresh air.

The same thing can be true for Phase I oncology research. An investigator can have the intent of learning about a new agent, but at the same time have therapeutic intent, the desire to benefit the child who is the subject in that context.

Commensurate experience, I would really ask the hard question: Is that a valid justification? The regs and examples talk about a bone marrow aspirate in a child who is used to having had bone marrow aspirates or biopsies before. One could see the same line of argument going toward the discussion of exposure to chemotherapy. A child knows what it is like to get chemo. What's the big deal if it is a commensurate experience for them to have another cycle?

Well, I would argue that it is a very big deal because children who have been through previous cycles have impaired organ function. The relative risk of that exposure to a Phase I agent may be higher. I am not arguing here that we ought to do Phase I oncology studies in healthy children certainly.

The flip side of this argument is the Catch-22 of the current scheduling of Phase I trials, which as most of you know, starts at a fairly low dose, so that the chance for direct benefit is relatively low, and some have argued for a dosing schedule in Phase I studies that actually starts at a higher level to increase that chance for prospect of direct benefit, getting back to the risk of toxicity one would expect a greater risk with that.

So, we have this direct relationship in Oncology between toxicity and efficacy that is going to be problematic no matter how we look at it.

The problems in defining benefit have been spoken about already. It may be more than just the tumor measurement that I mentioned earlier, and pain relief, improved quality of life, a sense of doing something when nothing else can be done.

These are all in a broader understanding of benefit, potential terms that can be understood as beneficial, and finally, pediatric altruism, I would echo what others have said, it does exist, and I think it is important not to forget that.

Finally, in Phase I oncology trials, we talk about risks and benefits a lot, but if one remembers the elements of informed consent, it is risk, benefits, and alternatives, and it is critically important that the alternative of hospice philosophy care be presented to parents, and most importantly, to the child, and this is really one of the terrific things about being a pediatric oncologist, having a long-standing relationship with a child who one can sit down with if he is 8 or 10 or 12 years old, and talk about hospice philosophy care as an alternative to Phase I trials.

Now, it is true they can be done in conjunction, but a real presentation of those alternatives to the child himself or herself, I think is what is critical to the informed consent process here.

[Slide.]

So, as I said, subject selection is not a

controversy. I haven't heard the first proposal for a new agent of anticancer drug in a healthy subject, and I don't expect we will hear that proposal. I think that it does qualify as research with the prospect of direct benefit, which puts it in a different category than those situations we are talking about today.

Finally, the potential for benefit mitigates, but does not eliminate the need for protection from research risks. I think it is really important that we don't abandon the paradigm of protecting research subjects from risk. We are in the midst of a major swing toward clinical research. I think that is good, but if we forget some of the lessons of history that Jeff spoke about earlier, we are going to get into trouble, and this potential for benefit does mitigate, but does not completely eliminate that need to protect kids.

[Slide.]

Subject selection then in studies with no prospect of direct benefit, a new acronym that I hope Bob Levine would like, PODB. Children without the target disease is probably another way, I would say, of saying studies without the prospect of direct benefit.

A Phase I cancer trial would be excluded here based on what I have just said, but a new antibiotic, a pharmacokinetic study in a new antibiotic in a child with cancer is potentially included. This is not true if the child is febrile and neutropenic.

This would be a dosing study in a child who was not febrile or neutropenic, but it is potentially a study with no prospect of direct benefit to the child who has cancer.

The differences between healthy children, kids with acute illness, and kids with chronic illness needs to be spoken of, and this is a generalization, and I have to make it clear that it's a big generalization, but at least it sets a framework, I think, that kids with chronic illness usually are better able to participate in a decision than the other two.

I would put healthy children in the middle, and most often someone with an acute illness or perhaps even an acute exacerbation of a chronic illness, but that gets tricky. A new onset acute illness or newly diagnosed child with leukemia may be least able to participate because of the sense of shock.

There will be exceptions. Certainly I have taken care of kids with cancer who regress rather than advance in their maturity, but most of them are able to make better decisions, I think, than their contemporaries.

I am going to spend the last few minutes running through some of these scientific, practical, and ethical issues as they relate to these questions of subject selection when there is no prospect of direct benefit.

[Slide.]

A couple of the scientific issues. I was on call last month and got a beep from a research nurse who asked me if it was all right to approach parents of a child with sickle cell disease, who was admitted to our hospital with pain crisis, for a pharmacokinetic study of a new intravenous preparation of an antifungal drug.

It struck me, first of all, as the attending physician for this child, that he was at virtually no risk for fungal disease--children with sickle cell are at risk for bacterial disease certainly, but not fungal disease--and that his hepatic function was probably not normal. In fact, I remembered rounding on him in the

morning and seeing that his eyeballs were yellow, to us lay language.

So, I was interested in this idea that a pharmacokinetic study would be proposed on this particular child who had altered liver metabolism, and was also on other medications that might have a drug-drug interaction.

It is important to remember that some diseases can alter these metabolism and disposition issues, and from a scientific standpoint, perhaps healthy kids are better subjects for these early studies.

It is also important to balance that, however, with what I want to call the rule of economy in research design, which says that good science requires the use of subjects that are going to be able to maximize generalizability. I use the word "use" here again I think similar to what Jeff said. Maybe it is all right to just recognize that we are using children and talk about it in a more frank fashion that way.

This rule of economy says that the minimal number of subjects should be used when we are clear that the goals are really to help future patients. It is a

best use of our resources sort of argument, and it raises questions about whether to use healthy children or sick children in these situations. If one anticipated that the drug one is studying is going to eventually be targeted toward a particular disease, this rule of economy would suggest that we ought to do the early non-beneficial studies in children with that disease.

[Slide.]

A couple practical issues broadly framed as geography and access. It is seductive, I think, to put sick children on these sorts of studies because they are already in the hospitals, and let's face it, that's where the pediatric investigators happen to be.

Their baseline labs are available, they have past medical experience. The slogan that there is no need to reinvent the wheel, and something mentioned earlier, I think very important, about the access to emergency medical services in the case of an anaphylactic reaction or something that severe.

So, this is a practical issue arguing for the preferential use of sick children in this context. It is not an insurmountable issue, however, because one could

imagine the construction of free-standing pediatric research centers with all of those things available, a lot more costly, a lot more impractical, but it could be done if it was decided that it was important enough to do.

Secondly, a practical issue is access. By this, I mean access to the intravascular compartment. Kids with acute illness often have an IV line, kids with serious chronic disease may have a central line, and I think compared with children who are not sick, the burden is relatively minimized in children for whom access is already established.

For a peripheral IV, I think the issues are less significant than having to put in a central line. One imagines, hopefully, that it will be considered more than a minor increase over minimal risk to take a child to the OR and put in a central line for the sake of a study without the prospect of direct benefit with no other issues going on.

So, these practical issues, in general, I think do sway us toward wanting to consider first children who are sick.

[Slide.]

Aha, this slide talks about the ethical issues, which I think would say, as Tevya says, on the other hand. I think "best interests" has been used a little bit this morning, but I just wanted to say that there is a limit of our best interests standard thinking here, and I want to be clear that a narrow understanding of the best interests standard would prohibit all of the research that we are talking about today. I think that a broader understanding of best interests standard is acceptable here, but we need to be clear that we are broadening it and perhaps to sin bravely, in Paul Ramsey's words.

A term that has not been used, and I think is critically important, is the therapeutic misconception. It has been reported clearly by Paul Applebaum and others in the adult context, it has not been talked about much in children, but there is no reason to think that things should be any different for kids than adults, and a real ethical advantage of doing these sorts of studies in healthy children over sick children would be to avoid the therapeutic misconception.

Collateral benefit is an interesting issue that has been covered already. I think there is some moral collateral benefit to raising children as altruistic beings, and finally, I get to the imperative of protecting sick children compared to protecting healthy children, and this is an argument from justice, which says that there needs to be a fair sharing of burdens and benefits, and in that context, I think children who are sick are already experiencing a great deal of burden.

Some of the burden should be shared by children that are healthy, and this argues from an ethics perspective for including those children in these studies.

So, I would conclude with what I would consider a vigorous rejection of the tendency for us all to say, well, that child is already sick, let's just go ahead and do the research anyway. I think we need to be clear about that, that risks making sick children even more sick, and I would psychoanalyze this a protective urge that I have for my patients that are sick, who really shouldn't be made sicker just because they are already sick.

Justice, as I mentioned, calls for a sharing of the burdens and benefits.

[Slide.]

This states the need for balance, that real world decisions require that we think about all three of these - scientific, practical, and ethical consideration, and in the end, what I hope we would come out with would be a reasonable admixture of studies on children that are healthy and children that are sick, but a diverse portfolio based on the particular clinical study that is being proposed.

Thanks.

DR. CHESNEY: Thank you very much for your comments and brevity.

Any questions for Dr. Kodish?

[No response.]

DR. CHESNEY: If we could return from lunch by quarter of 2:00, please.

Thank you.

[Whereupon, at 12:43 p.m., the proceedings were recessed, to be resumed at 1:45 p.m.]

AFTERNOON PROCEEDINGS

[1:50 p.m.]

DR. CHESNEY: This is the Open Public Hearing. I have comments from two people that wanted to have their comments read, and Dr. John Wilson from LSU, Shreveport, who is a member of the PPRU there had asked if he could say a few words, so why don't we start with Dr. Wilson, and then I can read the other comments.

Open Public Hearing

DR. WILSON: Thank you very much. I am John Wilson, LSU Medical Center, Shreveport, Louisiana.

I have listened this morning to a discussion of many issues which I have grappled with over 30 years of doing clinical trials in children, and it is really quite rewarding to hear the rather erudite and thoughtful approaches to many of these issues, none of which I believe have an answer per se, but each one is a struggle.

If I could take a few minutes of your time, I would like to make some comments and put forth some questions, and perhaps that will drive some considerations later.

First of all, the number of children likely enrolled from the FDA figures this morning were about 15,000 children needed for some studies to date. I would like to put on the table that you can multiply this figure by about 10 in general, because it takes about 10 children screened for basic inclusion criteria usually to produce one enrolled child. So, that is a general figure, 10 to 1, so you are probably looking at 150,000 encounters to produce the 15,000 children.

Now, in view of societal differences in participation of children in research, I was able to spend a little over a year in Sweden at the Karolinska doing pediatric clinical trials, and so I could compare that experience with the experience in the United States, and I can tell you from a personal experience which other of my colleagues have had as well, I might say, that there are societal differences.

For example, in Sweden, if you ask a parent for participation of their child in research, then, the parent regarded it as a privilege to have their child participate, and oftentimes the question of compensation did not come up, but they are not doing their best for

society if their child did not participate because, indeed, they viewed it as their opportunity to share the burden.

Recall that pediatric research is opportunistic and requires extensive manpower considerations, and there are a few pediatric clinical pharmacologists that have had formal training in this regard, so the question of use of normal children, if you will, I think needs to be viewed in that perspective of an opportunistic approach to studies.

For compensation, this is a matter that has troubled me frequently because I have never known how much is enough or what is too little, and I think this impacts upon the difference in our country versus Sweden and other countries, as well.

One thing we pin our compensation to, in addition to out-of-pocket expenses, is whatever the prevailing minimum wage is, and we do this to give people a choice. They can either accept the "minimum wage" or they can go down the street and make more. All right. So, at least that gives some kind of anchor post.

For compensation, let's recall that for children

seven and younger, that may make no sense at all, because they may not care. As a child ages, and especially adolescents, who want to go down to the corner and buy those five CD's that they have been waiting to purchase, compensation becomes more important, so I think an age determinant is important to realize.

I think we must also give attention to support of IRBs and their infrastructure, and especially as we focus more on assent and some of the things mentioned this morning. This whole matter of IRB review at most institutions, I believe, is grossly underfunded and undermanned.

I would support some kind of uniform or harmonization of rules by which all IRBs operate. I am aware of differences, important differences in the way some private IRBs operate versus university IRBs, and I think that if I had to stand here and bet you a case of Coca-Cola that that is where the main pitfall and trouble is going to surface in the next few years, it is going to be in all IRBs not conforming to the same guidelines.

I think we need to make that a happening very soon.

The dollars, shortened timetable of protocol review and performance, such that outcome rather than ethics of design and care of subjects drive a study forward for reward of the sponsor, performing institution, and investigator all too often.

I would propose remedial measures to include the following: emphasize quality of a few studies and the data from those studies, de-emphasize quantity of studies. We don't necessarily need to study the 16th Ace inhibitor in children unless it offers some benefit, as an example.

I think we need to increase the institutional infrastructure for the IRB and other administrative items consuming investigator attention away from needs of the child subject. Those of us that are in the trenches doing research are increasingly burdened by administrative items, many of which are to stay in compliance with state and national regulations, and the more we are drawn out of the trench and behind the desk to handle these items, I submit to you that the less attention and care we can give to welfare of the research subject. This is happening.

Let me put something finally on the table for your consideration of risk. I have heard minimal risk, above minimal risk, and so forth. Let me ask you if we should have a focus or do we have a focus at the right level of concept on this matter?

I submit to you the following: I question the magnitude of risk being it adverse effects, i.e., safety, or lack of efficacy, which by the way, is a risk, for use of unproven drug versus risk of proving or no safety and efficacy in study subjects.

Now, once we make that determination, i.e., the risk of continued use of an unproven drug versus proving or not via a study, utility of the drug in a child, once we make that determination, then, we can turn our attention to benefit and add questions of benefit to the balance.

Now, this is a little bit of a different twist on our concerns with risk, but we have heard a lot about only two-thirds of drugs are approved for use in children, and many of these drugs continue to be used in children, well, what is the risk of doing that, what is the risk of not knowing the dose, the risk of inefficacy,

the risk of adverse effects, and so forth.

It is very, very hard to get a handle on the magnitude of that risk, and I realize that. However, that is going on every day. What is that risk versus the risk of doing a well-designed study carefully in a child?

Now, if it is more risk to do that study in a child, then, I think we must carefully examine the study, but until we can reconcile the risk that is out there in the wild state right now with the risk of doing a study, I believe that our consideration of the balance of benefit is a bit loose.

So, I would offer to you to consider that redefinition of risk, if you will.

Thank you again, Dr. Chesney, for allowing me to make these comments.

DR. CHESNEY: Thank you very much.

We have a statement from Susan Weiner, who is President of the Children's Cause, which has been handed out to everybody at the table, and I didn't know if Susan wanted to make a comment or not.

DR. WEINER: I don't want to make a comment about that statement, thank you, Dr. Chesney. I wanted

to make a comment that was more appropriate to the context of this meeting this morning.

I am President of the Children's Cause, which a pediatric cancer advocacy group that is parent based. I was a parent of a child with cancer for many, many years, and I was also, in my former life, a research developmental psychologist, so the issues here discussed today are of interest to me from both perspectives.

The point I want to make briefly about today's meeting is that I would hope that everyone's considerations would remember that these issues are very, very context-sensitive, that the issues of benefit/risk/assent are all dependent on the developmental variables, as well as whether or not the kids are healthy, moderately ill, or chronically ill, and with respect to kids with cancer, kids who are chronically ill, I think that the notion of commensurate experience is a very tricky one.

Many of these kids are hospital traumatized, as you well know, and adding additional burden is a very serious consideration, and related to that is also the fact that there is, under those circumstances, a

temptation really to do more research partly because they are captive, but partly because they are interesting.

In that sense, I believe there is often an intense investigator or physician, caretaker conflict of interest that obtains.

So, I felt obligated from both perspectives just to stand up today and to make comment about those issues to this very distinguished panel.

Thank you.

DR. CHESNEY: Thank you very much for those heartfelt comments.

Dr. Zametkin had to leave. He will be sitting at the table in our session tomorrow. He is at the National Institutes of Mental Health. I will try to extrapolate the information he gave me.

He says, number one, that the Code of Federal Regulations is antique, that it has no mention of normal controls, it was based on 9-year-olds, and we need to spend more time reviewing how it would pertain to 16- and 17-year-olds, and he feels that the whole Code of Federal Regulations needs to be redone for the modern world.

He says in the last comment that minimal risk

for a 9-year-old is very different than minimal risk for a 14-year-old or a 17-year-old, and that these need to be developmentally appropriate.

He also strongly emphasizes what Dr. Wilson said, which is the real risk is, as we all know, that millions of children are being treated with drugs for whom no studies have been done. For example, he deals with ADHD, and he said that clonidine was developed as an antihypertensive, and I think I am correct in saying that it has never been tested for children with ADHD, and yet there are thousands and thousands of children taking it.

He says it is very sedating and we don't know the long term risk. His last comment was that there is another population of healthy children who might be willing to participate in studies, and those are the siblings of children who are ill.

Those were the comments that he wanted relayed to the committee.

Committee Discussion

DR. CHESNEY: Our next and greatest challenge is to address the questions that Dr. Murphy and her committee have given to us. What we tried to do over the

lunch hour was to give approximate times that we would allow for each question based on what they felt to some degree was the complexity of the question.

We have allotted approximately 20 minutes for the first question. They would like a consensus vote from the committee, but they point out that everybody at the table can ask questions or make comments, and so let us proceed with the first one, which they felt represented the simplest possible scenario.

Case Study No. 1

DR. CHESNEY: A manufacturer who wants to taste test a new elixir formulation of an antibiotic that has already been approved for use in adults. The intended study population is asymptomatic, healthy children. The idea is to provide each child with a single dose, observe them for an hour for reactions, and then, if they can, answer a short questionnaire, provide the information about taste tolerance and palatability.

We have five parts to this question, which means approximately four minutes per part.

A. Does the study exceed the threshold of a "minor increase over minimal risk"?

I wondered if it would be helpful just to define what are the risks first in this particular scenario. Would anyone like to comment on whether there are any risks to this testing?

Dr. Edwards.

DR. EDWARDS: I think that one risk would be that the child would have an anaphylactic reaction to it or an immediate adverse event associated with it, perhaps less likely if it is a totally new compound, but if it is related to other compounds, penicillin derivative or something of that nature.

I think the other theoretical risk is whether the patient could conceivably have some antibiotic effect, so that there would be suppression or development of resistance, although that would be less likely to occur, but i think is a realistic opportunity if the medication was going to be used for a longer period of time, and certainly in this time when we already have bugs that are already too resistant, that is a problem, as well.

I think other untoward adverse events that we couldn't appreciate are also a possibility.

DR. CHESNEY: Wearing my Infectious Disease hat, the issue of a single dose of chloramphenicol causing damage comes to mind, and also I think depending on the half-life of the antibiotic, if it was something like trimethoprim sulfa with a very prolonged half-life and potential for bone marrow suppression, and the drug were around for three or four days, that might be another potential risk.

Do other people want to pose risks? Yes.

DR. FINK: It is not exactly a risk, but I think this brings up the issue that when we are trying to do this, if we say that pediatric research is a limited resource, one could also argue that just doing a palatability or taste test on the drug, you are exposing the children to the risk, but not gathering the maximum amount of data, and this study should rightfully be combined with a pharmacokinetic study, so that you maximize the data you collect while keeping the risk minimal.

DR. CHESNEY: Excellent point.

Yes, Dr. Fost.

DR. FOST: I would just expand on that and

suggest that it ought to be combined with a clinical trial, that is, if the study were done in children who had an infection who might benefit from it, then, you don't have to be bogged down with the minimal risk issue, and you get even more mileage out of it.

DR. CHESNEY: Dr. Ward.

DR. WARD: Probably not a large one, but the excipients in the elixir have to be considered as well as the parent drug with respect to adverse events.

DR. CHESNEY: Thank you. Yes.

DR. SPIELBERG: It is very much dependent on the knowledge of the compound itself and the class of the compound. You can't even start assessing risk without knowing the biochemistry of the compound, the toxicology is, whether or not anaphylaxis ever has occurred in this compound in the adult population, so you have to know a lot about the compound to start off with.

The second issue is that in order to initiate a clinical trial, we have to know something about the PK of the compound, and, in fact, if we began a therapeutic trial with a compound that exhibits increased clearance, as many drugs do in children, we might end up

underdosing, therefore, failing to treat the kids adequately, coming out with a negative clinical trial, and, in fact, maybe enhancing resistance.

Often we do have to do a single dose PK trial to understand the handling of the compound, sometimes we don't, but often we do.

The other issue is that in terms of the benefit to the kids, and in terms of development of resistance, formulation acceptability is probably the sine qua non of compliance.

We have struggled over and over and over again about drugs that theoretically are great, like the semi-synthetic penicillins, which are so bad that the first dose goes in, the second dose goes on mom's dress, and that's the end of the bottle.

What you have done then is failure of treating the child, and then secondly, ending up with the potential of development of resistance, because compliance is bad, so that there really is a major goal to getting formulation right.

However, if this is a formulation just of another me-too drug with the same spectrum as every other

drug, then, that changes your approach again. If this is a novel agent with a lot of potential benefit in children, but it is really foul tasting, our chemists cannot make good tasting molecules these days, that is a rule of thumb, they are also insoluble, that in order to produce a pediatric formulation, then, there would more of a drive to do it, and if it's a me-too, then, maybe risk becomes a little bit more prominent.

DR. NELSON: The other question I would ask is if bioequivalence has been established and whether or not bioequivalence could be established in the adult population, raising the question whether the formulation itself changed absorption characteristics. I am assuming that that would be addressed before you even gave it to a child.

DR. SPIELBERG: And bioequivalence we argue really should be done in adults. That is again something that can be done in the adult population, does not necessarily have to be replicated in children unless there are issues of particular pediatric food interactions, like formula or such.

DR. CHESNEY: One more comment and then we have

already exceeded our four minutes.

DR. SZEFLER: I think adding features onto the study may overcomplicate what was designed as a simple study. I mean a company has maybe 10 preparations, and they just want to see which one the children feel taste the test with the active compound being in there because that is the most troublesome.

I think to add a lot of features on may add more risk than necessary to answer the question that is just a screening question.

DR. CHESNEY: Could we vote on your comment, which is that this was intended to be a simple question, but with Dr. Murphy understanding all of the caveats that were mentioned.

Does anybody feel that this would exceed the threshold of a minor increase over minimal risk? Please raise your hand.

Great. Consensus on the first one.

The second question. Would any precautions or exclusions minimize risks that we have already discussed? Comment. Dr. Nelson.

DR. NELSON: I would like to just raise one

general question, which didn't affect my vote on A, but that's that I don't think if our intent in using the language "minor increase over minimal risk" is to say that this would have been appropriately considered by an IRB under 46.406, I think that is wrong, that, indeed, the proper threshold here would have been minimal risk, and that should have be considered under 404.

Now, having said that, I would approve this as minimal risk, but I don't want us to assume that that is the correct standard and that IRBs would evaluate it under that category.

DR. WILFOND: There is no benefit. I mean why would you think this would be considered as prospect of--

DR. NELSON: 404 is no prospect of direct benefit, minimal risk research. 406 is no prospect, minor increase over minimal risk.

DR. WILFOND: Okay.

DR. NELSON: I think the more general issue is the extent to which Subpart D is or is not part of the approach within the FDA, as well, which I think is sort of a sub-theme in all of this.

DR. CLAYTON: One other comment that I would

make is that it seems to me that it would be important to do this study in the bigger child first before you do it in the little child, because just giving medicines to 6-month-olds is really, you know, not fun for the mother or for the child. So it would make sense to test this on a child who is big enough to give you a firm opinion before you give it to the baby.

DR. CHESNEY: I think that comes up under C.

Any precautions or exclusions that would minimize risk? Yes.

DR. SPIELBERG: There is a fairly good literature on taste testing in kids and the volume of liquids that you need to obtain adequate data. One way of avoiding giving full doses of the drug would, in fact, be to give a very low dose of the formulation sufficient to get the answer you want, but not necessarily give a large dose of the drug. So, that is one way of minimizing the amount of drug actually administered to the child.

DR. CHESNEY: Dr. Danford.

DR. DANFORD: It is almost self-evident, I guess, but you would probably want to take a brief intake

history to determine whether or not there had been a prior adverse reaction to a compound of a similar nature.

DR. CHESNEY: Reaction to a dye.

Dr. Kauffman.

DR. KAUFFMAN: It struck me that one-hour observation might be a bit short to pick up all adverse events that might occur after this exposure, so you may want to build in a phone follow-up or something to see if there is a delayed adverse event.

DR. CHESNEY: One more comment.

DR. WILFOND: If we think of minimizing risk as also essentially altering the benefit-risk ratio, I think it comes back to the point that was made before, about trying to do a study like this somehow in conjunction with great opportunity for benefit, such as combining with a therapeutic or a PK study, as well.

DR. CHESNEY: Absolutely.

DR. EDWARDS: I second that because I think one of the things we are also trying to do is to tell people that they shouldn't use medications no matter what they are in a way that is not beneficial to them or therapeutically helpful. So, I guess I do sort of have a

discontent with the study and really kind of applaud using it in a patient who may need the medication as opposed to just being a taste test.

DR. CHESNEY: Thank you. I think we have defined that.

No. C. Could this study be done in children who cannot give assent, on other words, the infant and toddler, up to 7 years of age?

Comments? Yes, Dr. Nelson.

DR. NELSON: I would agree with Ellen's earlier comment that you certainly would want to start with children who could assent, but if you think that assent needs to be placed in the context of parental permission, and you have a parent who is going to do much of the risk-benefit assessment, if you are taste testing an oral antibiotic, I would assume that assent is a given if the child puts it in their mouth, so that you are certainly not going to force them to drink it.

So, you know, depending on what we think assent is and how we define it may affect how we would answer this question. If what we are saying is we wouldn't force the child to drink it, I think the answer is

obviously yes.

DR. CHESNEY: Dr. Luban.

DR. LUBAN: I think you might also, if you were going to do it in younger children, make sure that you had an adequate tool to assess the taste methodology and such validated kinds of devices do exist, so you would have to build that into the protocol.

DR. CHESNEY: Thank you.

DR. WARD: I would argue also that it is exactly that younger population that is most problematic to treat because you can't reason with them frequently. So, using that tool, including it in the trial may be very important if that is an antibiotic that will be used in that particular age range.

DR. SANTANA: I was going to comment that actually that is the purpose of doing this because ultimately, the ones that will potentially benefit from this new preparation are going to be the infants and toddlers, and not the teenagers who can take a pill or can take the adult type vehicle.

So, although I agree that we have to start with an older population, eventually, we do have to work down

to the younger population because that is in essence where the tests will be carried out, whether it works or not.

DR. HUDAK: And the other observation is basically that having brought up children, and so forth, just the fact that they like something when they are age 10 doesn't mean they are going to like it when they are age 3.

DR. RODVOLD: The other comment I would make is that you may have to test a couple of ways to deliver this. My wife actually does research in this area. Whether they use oral syringes or other devices that have recently been introduced, and put them in as part of it, so that you can tell that, and then she actually has a scaling that is judged by independent people, and you have to get into some other things like who is holding the child, who is giving the drug. There is lots and lots of variables that you have to include from getting the drug in, as well as what happens after the drug is put in their mouth.

DR. CHESNEY: Thank you. Very helpful.

Would everybody agree that this study could be

done in children who cannot give assent?

Okay. Move on to D. Would it make a difference if the children had a disease potentially responsive to this antibiotic? Comments?

DR. FOST: As I said before, I think that should be the presumption. I don't why everything that Dr. Spielberg said couldn't also--I mean whether you want to combine it with the PK study or no, but I don't see why all the subjects in this trial can't, in the development of this drug, be children with otitis or whatever it is that the target is, so at least you have some prospect of benefit.

DR. SPIELBERG: Again, it is timing in the development process. We are assuming here, because we are going to do everything subsequently with this same formulation, this is going to be the basis of registration of the drug and labeling, that we want to do all the studies with the right formulation, but we also want to do it at the right dose, so when we are doing the taste test, we don't know what the dose is.

The risk, particularly in small babes with rapid clearance, we are going to underdose and therefore, we

really don't want to start a clinical trial until we know what that dose is.

DR. FOST: I didn't mean to imply that you had to be part of the clinical trial, but why can't you do your taste test in children with otitis or whatever it is you are seeking, the target audience that this drug is.

DR. CHESNEY: Susan.

MS. KORNETSKY: I would like to also just say from an IRB perspective, I can't see an IRB looking at this without asking the question, the initial question, why do you have to do this in normal children initially.

I mean I have to agree that I think there are other populations of children that could potentially benefit, and we may decide that it's minimal risk, but I think that question has to be answered. I couldn't see IRB approving this.

DR. FOST: The advantage is that it at least gives you the advantage of the class issue, that is, you are doing it on a class of children, then, who presumptively might have consented because they are children with infections, preferably recurring infections, so that if they could understand what was

going on, they might reasonably want to participate in a study like this, because they could be beneficiaries of it. A normal child might also, but the probability is just much lower.

DR. HUDAK: I think in terms of considering the child with the otitis, there are several other issues that are involved. One certainly is that the physician is not going to withhold current standard effective therapy, so this would be something that would be added on top.

DR. FOST: Understood.

DR. HUDAK: There are issues, then, that have to do with drug-drug interaction and multi-drug resistance, and things of that ilk.

DR. FOST: I understand all that. It might be a child with recurrent otitis who is between infections or recurrent UTI who is uninvolved at the time. It just gets at this issue of whether the child is part of the class of persons for whom volunteering for a study like this holds at least some prospect of benefit.

DR. FINK: I would maintain, though, there are very few children who don't get at least five or six

courses of antibiotics during their childhood, and so you can get rid of some of the academic posturing and just say most all children will be eligible for this because they are likely to receive antibiotics at some time during childhood. I think we are almost making it too complicated.

DR. SZEFLER: Could I just follow up on that question? You said your IRB wouldn't approve it, and then you voted no on A. Why would you vote no on A and say it was more than minimal risk?

MS. KORNETSKY: I wouldn't say that it is more than minimal risk, but I think you need to look at the reason that a study is being performed and if it's an appropriate population.

I mean categorization of risk is not the only reason why an IRB would or wouldn't approve something. Just because something is minimal risk may not be the reason that they would approve it.

DR. SZEFLER: But it's a simple taste test with an active drug.

MS. KORNETSKY: It's giving a child a drug who does not need it, and it is not in a class--

DR. SZEFLER: So, would vote yes on A?

MS. KORNETSKY: No, I would make a decision outside of risk.

DR. NELSON: To jump in the IRB issue, this is complex. I mean you are strictly correct. If something is judged minimal risk, there is no tying of that to either benefit or for that child being in a class which that condition would provide generalizable knowledge. There is no discussion of condition or benefit under minimal risk research under 404.

But if you want to maximize the chance of your IRBs, that you are going to go out and send it to, to approve it, you either find an opportunity to argue that there is a prospect of direct benefit, although I am less convinced that you could succeed on a taste test in doing that or you have to say that it's a minor increase over minimal risk, in which case it does not need to be a direct benefit, but the two are related.

There are IRBs who would approve it under minimal risk without concern of condition, which might be mine, and there are IRBs which would not, which is clearly Susan's.

DR. SZEFLER: I think what the FDA wants is directive on this, because what they are going to walk out of this meeting is to say for this kind of a study, it's not minimal risk, if that is what your IRB is saying.

MS. KORNETSKY: No, I am not saying that. This is minimal risk, and what I am saying is our IRB would probably not approve this for other reasons, not with minimal risk. I have no questions, this is minimal risk. Just because it is minimal risk doesn't mean that we necessarily have to approve it.

DR. WILFOND: I want to make two comments. First of all, on the risk issue, we have already discussed that. I think that the reason why, in my mind, this was a minor increase over minimal risk was because it would be unlikely the possible concern about anaphylactic reaction, which I think still means it could be approvable, but I would at least not just call it minimal risk.

I really want to get back to this question about patients having the disease. It is just not clear to me whether or not having had otitis once or twice or three

times really will have any direct impact on the risk-benefit ratio for this particular child.

It seems to me that either child could be a suitable candidate for a study like this.

DR. CHESNEY: I interpret it in the same way that you did, that giving one dose as a taste test, it wouldn't matter to me whether the child had otitis media or not.

I think the other issue is whether you could do a more detailed study using those children, so I interpreted it the way you did. We are getting short of time.

Could we come to consensus on D? Would it make a difference if the children had a disease potentially responsive to this therapy? Does anybody say yes?

DR. FOST: Yes. It makes it easier to justify it.

DR. CLAYTON: I want to make one other comment about this. It depends on the antibiotic. I would feel differently about doing a taste test with ciprofloxacin than I do about yet another, you know, beta lactam, so, you know, it would just make a difference about what the

potential risk profile in the child would be, or, you know, an IV drug that was related to vancomycin as opposed to an IV drug related to penicillin. I would feel very differently about those drugs.

DR. MURPHY: Joan, let me hopefully simplify a little bit of this. One of the reasons that we emphasized that these are approved products in adult is that we know some of these things that people brought up about them, maybe the class of drugs.

So, to have gotten to this point, I will ask you to assume that we would not have done a taste test even someone for cipro, I mean where we know we have certain risks that might be applicable to the child.

So, for these scenarios, when you begin the question, now, when you get down to the disease part, but in the beginning, we are asking you to think of these in which we have other data, because that is really the situation that we are in right now.

Many of the products are approved in adults and we have a fair amount of information that would allow us to identify the risk.

DR. CHESNEY: Thank you, Dianne.

For just the voting members, is there anybody that feels that it would make a difference if this child had a bacterial infection and received one dose of antibiotic?

[No response.]

DR. BOTKIN: I think I would like to clarify what I think Norm is saying in part about this issue. It seems to me we have got at least three levels - one in which the dose of the medication itself during a taste test may be therapeutic for that individual child. I don't think we are talking about that with a single taste test, but there are those kids who may benefit at some point in the future. That doesn't make this a therapeutic trial, but it seems to me it is still a strong enough justification for including those kids who may themselves eventually benefit from the drug versus kids who may have no apparent need for that drug in the future.

DR. CHESNEY: Thank you for the clarification.

Finally, in E, would it make a difference if this were an investigational drug and we did not have any information about toxicities or dosing, we have no

information from the adult population to extrapolate to children? Would that make a difference as to whether you would allow an asymptomatic healthy child to be involved in a taste test? Comments.

DR. FINK: When you say "no information," does that mean that it's not FDA approved, because if you looked at the rule, it would say that this trial would rightfully take place at the early part of Phase III trials in adults in the future, so it wouldn't be FDA approved indications in adults, but there would still be a lot of data available.

DR. MURPHY: That is a good point. In other words, that would be the situation. It may not be approved for this indication in adults, but it may be that--or a new molecular entity that is being studied, which you know will be used in kids, and we may have some data, but certainly not the amount of information we would have if this were an approved product that had been out there in the market.

So, you are right, there is going to be a spectrum of how much data we have. What we are trying to do is make the cut. We don't have all that postmarketing

information. Is that where the shift comes or is it further up in the drug development process?

DR. CHESNEY: Dr. Nelson.

DR. NELSON: I think key is how much information is available, and if there is sufficient safety and perhaps some efficacy--I mean if you have already decided that you are giving a low dose that is potentially sub-therapeutic, and simply interested in taste, the efficacy data is not as important, but certainly the safety data would be crucial to decide even if that low dose were safe enough to do a taste test.

So, at best, you would be looking perhaps at somewhere after you have done--you know, if you are talking in children without a condition, where you are not designing for potential benefit after you have done at least all of your Phase II and perhaps a fair amount of your Phase III testing.

DR. CHESNEY: Other comments? Dr. Gorman.

DR. GORMAN: I am going to start the "it depends" litany for the rest of the afternoon. I think it would depend on what the indication for this new agent was, whether there were alternatives and the safety data

that has already been--if this was a promising new antibiotic for a resistant organism that was prevalent is pediatrics, you would be much more willing to approve it on the basis of potential benefit.

If it was a me-too antibiotic in a class that we already had multiple effective alternatives, the answer would probably be no until more data was available. So, it depends.

DR. CHESNEY: Could we then say, the voting members, does anybody feel strongly that you would not use this investigational drug in a healthy, asymptomatic child, or should we say it depends? How many would feel very comfortable using this drug in a taste test in children? Please raise you hands.

No one is comfortable with that.

Let's move on to No. 2.

Case Study No. 2

DR. CHESNEY: A sponsor has developed a new formulation of an anticonvulsant which is approved for use in adults. The intended study population again is asymptomatic, healthy children. The study design is to give one dose, observe, and obtain one or two blood

samples for a pharmacokinetic study.

The first question for which we have five minutes, is: Does this study exceed the threshold of a "minor increase over minimal risk"?

Let me start by asking what risks people would be concerned about for this anticonvulsant in healthy children.

DR. KAUFFMAN: Again, this comes back to Steve Spielberg's comments. It depends a lot on what this compound looked like and what its safety profile was in preclinical, as well as early adult clinical studies, but if it's like a lot of the anticonvulsants, you could be concerned about everything from bone marrow suppression to other idiosyncratic reactions, to long-term ophthalmic damage, and a whole slue of things, in addition to the direct CNS effects.

So, I think there would be a number of theoretical concerns that might not be true for a specific compound.

DR. SANTANA: The other thing I would be interested in knowing is what this new formulation is all about, is this another IV formulation that has already

been tested, is this a new PO formulation. I think that kind of information would help me determine what the ultimate risks for the patient would be.

DR. CHESNEY: That is a good point. It doesn't state whether it's oral or intravenous. Susan, I would be interested in your thoughts.

DR. MURPHY: Let's just say it's oral, so we can facilitate the discussion.

DR. CHESNEY: Dr. Fost.

DR. FOST: To me, the question of increase over minimal has to do with the venipunctures, not the drug, and that would vary with the child. That is, for a child of a certain age, who is hysterical about a single shot or a single venipuncture, two venipunctures that they don't need is way more than exceeding that standard.

For a child that is quite complacent and accepting, and for whom it is minimally uncomfortable, it would be okay. So, it needs to be child-specific.

DR. CHESNEY: Susan.

MS. KORNETSKY: I think you can probably guess that if I had problems with the first one, my problems are very much concerned about this one.

Is this a minor increase over minimal risk? I mean I think there would need to be a lot more information about the particular drug. I think this number of venipunctures for a child absolutely, probably is a minor increase over minimal.

I mean to me, as stated, this clearly falls in the category of research that even if it is a minor increase over minimal, I can't see how the rest of the conditions could be justified, and this to me would seem like something that just could not be approved or had to be sent to an expert panel or whatever.

DR. CHESNEY: Thank you.

Dr. Gorman.

DR. GORMAN: This is a therapeutic area where I would be swayed by an alternative argument that I have no good alternatives to treat children with, and would be willing to consider potentially more risk for children knowing that my therapeutic options for treating convulsions in children are poor.

DR. CHESNEY: Dr. Ward.

DR. WARD: I think you have to justify why you had not studied this in children who already have

seizures.

DR. FOST: I want to take one more crack at it, Joan, because as often as it has been said, I am not sure everybody has gotten this point yet.

The issue is the role of a parent in this situation--forget the IRB for a minute--is to make their best guess--in my view--is to make their best guess of what the child would decide if he or she had a moment of lucidity, I mean even a two-year-old, could understand everything in the way that a competent adult would.

A competent adult with a seizure disorder, knowing that you run out of ways sometimes in treat seizure disorders, might say I will go through a lot of inconvenience and pain and discomfort and risk for a non-therapeutic study, for a PK study of a new drug on that far-out possibility that you may hit a home run and two years down the road, I may benefit from this.

Even maybe as a class of people with epilepsy, I am willing to do this because I have a real deep interest in this. I think a parent could make an argument like that for a child with a seizure disorder.

It is not because they are going to benefit from

the single dose or even from a PK study, obviously, they are not, but it's that they can make a presumption that the child might be willing to undergo some inconvenience, even more than minimal risk.

So, that is why I would, for both of these studies, say they are just as easy--maybe it's a little bit harder to find the people--but they can be done from a clinical standpoint just as well in children with the disorder, and that is the moral justification for using that group of individuals.

DR. CHESNEY: Thank you. I feel like we are already coming to a consensus, so let me take Dr. Edwards and Dr. Spielberg, and then we will vote.

DR. EDWARDS: I think that there is a clear difference in this question than the preceding one, because if these are normal health children that do not have epilepsy, then, there really is not potential for benefit from the study, and I think that is an important distinction. I would feel very uncomfortable subjecting a normal healthy infant or toddler or child to this particular drug with no benefit in store for them.

DR. CHESNEY: Thank you. Dr. Spielberg.

DR. SPIELBERG: I concur. I think, you know, as opposed to the antibiotic situation where the vast majority of children will be exposed to antibiotics, at most, 1 percent of the population has seizures, it is going to be relatively rare, and the diseases, and the drug is probably indeed better studied in children with the disease entity to understand the effect of the disease state on handling of the drug.

With respect to the venipuncture issue, though, and this going to come down to here, we shouldn't confuse the number of samples with the number of venipunctures, and I think this really is key. If we are doing our job right, it should be one stick for all these samples.

DR. CHESNEY: Thank you.

DR. WILFOND: Joan, could I just add one point of disagreement quickly?

DR. CHESNEY: Yes.

DR. WILFOND: I think the reason why I might disagree--I have two reasons. One is in terms of Norm's point regarding what children would think in a moment of lucidity, certainly, there are adults who don't have diseases who do decide to participate in non-beneficial

research, so it is not clear that a child as an adult would not be willing to do that.

The second thing is that again we run into the problem of all the research falling on children who have the disease, and it seems to me that doing research on children who don't have the disease might spare the children who have the disease the additional burden of non-therapeutic research.

DR. CHESNEY: I think we may be even able to address that in B, but let me just see if there is a consensus on A.

Is everybody in agreement that this situation does represent more than a minor increase over minimal risk?

All right. Consensus about that.

Are there any precautions or exclusions that you feel would minimize the risk for an asymptomatic healthy child?

DR. FOST: This was discussed extensively by the National Commission, and it has to do with the presence of an active advocate, namely, usually, the parent. The risk here for me, as I said, is the child being phobic or

terrified at the venipuncture, and the presence of a parent who understands that any point they can say no, we are not doing this, I said yes, but now I am going to say no, because the child is sending some message that they really want to withdraw at this point, that reduces the level of risk.

DR. CHESNEY: Any other comments? Dr. Nelson.

DR. NELSON: I find it difficult to think about ways of minimizing risk unless I think about the participant population that we are particularly involving in the research.

So, for example, if we have already decided that we are not going to do this research in healthy children, then, my next question is how do we minimize risk in children who we would do this research in, which would be children who have seizures.

So, raising questions, I assume that it would potentially be an add-on therapy. I mean it raises a whole host of other questions about the proper design of that study to minimize risk, which are very different, having already answered the first question that it would be under Case 1.

DR. CHESNEY: My interpretation of this is, is there anything that could be done in the asymptomatic healthy child that would make you more comfortable with doing this study?

DR. NELSON: Obviously, I just answered that question by saying no.

DR. CHESNEY: Thank you.

Is there a consensus about that? Okay.

C. Could this study be done in normal, healthy, asymptomatic children who cannot give assent? I think the answer is no since we have already said no.

Would it make a difference if the children had the disease for which the drug is indicated in adults?

DR. FOST: I think that same question, though, should be asked about children with the disease. I think it is an important issue here that was mentioned briefly this morning, perhaps by Skip of others, namely, let's assume we are only going to do it in children with a seizure disorder for other reasons we said.

This issue of whether a two-year-old or a one-year-old or a six-month-old, who screams and yells, that is, who obviously vigorously dissents from having

this done, whether that should count for anything.

There seems to have been an assumption that once you are under this age of assent, that any kind of dissent should be just sort of discounted, that is, you can just overwhelm the child and say the hell with it, obviously, they don't want to participate in it, they don't want to participate even in regular immunizations or appendectomies or anything, so we are going to ignore them.

But where there is no benefit, I have to say I am troubled about the idea of just ignoring any kind of protest from the pre-verbal child. I realize there are subtleties there, but I think we should accept the possibility that there are some kids who at some point should not be forcibly restrained to engage in a PK study even though they have the condition.

DR. CHESNEY: Thank you.

Other comments? Yes.

DR. FINK: I think we are to some degree leading ourselves down that well-known pathway that is paved with good intentions, because if we follow this logic, then, we are not going to study anticonvulsants in children who

are below the age of assent, and most seizure disorders in pediatrics start in infancy when we most need the data.

So, we are going to have to give up on one area or the other. Either we don't do any of this research in the children who need it most, or are we allowed to say that children who can't give assent can be involved in research even if they don't like it, because the outcome is important?

DR. HUDAK: I would just like to echo that, that the only two-year-old child that you are not going to find giving you a fight with an IV is going to be one under general anesthesia.

DR. CHESNEY: Dr. Danford had a comment.

DR. DANFORD: I just wanted to perhaps extend the point that Dr. Fost made. In the specific setting where we are talking about anticonvulsants, we ought to be cautious not to make the equivalency of an age of assent and the ability to give it.

There are many intellectually impaired victims of a seizure disorder who might be beyond the standard age, but who might not be able to give assent in the

usual sense.

DR. CHESNEY: Thank you. Yes.

DR. BOTKIN: I would say there are some other issues, too, that have to go into assessment of harm with venipunctures. One, of course, is just the pain of the procedure itself, but with a five-year-old, you have got a lot of anticipatory dread, and you have got a lot of post-puncture anxiety that will persist with the child for a substantial period of time. I think Ellen described that with the nasal washings with her kids.

I would say that a poke for a five-year-old for those kinds of reasons ought to be considered substantially more burdensome than a poke in a six-month-old who screams when they hurt, but following that presumably the injury is gone.

DR. CHESNEY: Yes, Dr. Clayton.

DR. CLAYTON: I don't want to be understood as having said that I think that we need to defer to children's dissent all the time. I think that the question that is really before us is whether there are instances when the information that we are going to get is so valuable that we ought to proceed over a certain

amount of dissent and to avoid going down the road that someone across the way identified, and also paying attention to the fact that there are ways to make the experience less noxious or more noxious for the child, and so decrease their distress even if you can't limit it to zero.

I think if you really can't do research on a child who says no, then, no two-year-old is ever going to be studied for anything. I think that one of the things that I was trying to identify is that at some point we really have to face up to it and say dissent notwithstanding, are there times when we ought to go ahead anyway.

DR. CHESNEY: Thank you, Ellen.

If I could just try to summarize Issue D, is it fair to say that the voting members of the committee agree that it would make a difference if the child had a seizure disorder? We are in agreement about that.

Moving on to E, would it make a difference if, like scenario 1, this were an investigational drug, and we had preliminary information from adults, and that was all?

DR. MURPHY: Joan, when you ask that question, having answered the first A to the negative, we now will assume the kid has the disease when you answer--

DR. CHESNEY: Does have a seizure disorder, okay.

Yes.

DR. WALTERS: May I come back to D for a moment, because the question raised in B can also be applied to D. Even after you have narrowed down to children at risk for seizure disorders or with seizure disorders, there may be steps that can be taken to minimize the risks to those children.

For example, any group of adults for whom the anticonvulsant would be contraindicated should also--I mean the same criteria should be applied to the children. I am thinking especially of adolescent young women who might be at risk for pregnancy and therefore might be at risk for a problem with the fetus that they are carrying.

DR. CHESNEY: Thank you.

If this were an investigational drug and the children to be studied had seizure disorder, would our answer be different?

Yes, Dr. Nelson.

DR. NELSON: I am going to say they would not be much different, but unfortunately, I think the devil is in a lot of the details, as well. Just to briefly comment on assent, I mean if there is a therapeutic benefit that is potentially available to a child with seizures in the design of this study and eventual drug, then, assent could be appropriately waived, so that we wouldn't necessarily require it, and you would still minimize risks by trying to draw blood samples at times where there may be therapeutic sampling going on.

I think the threshold, if the amount of information available is less abundant, would be in the design. I think you would feel differently if this was simply a me-too drug versus a drug that is trying to treat seizures which have been refractory to treatment. So, whether it's an add-on study and the intent of the drug, the study design would make a big difference as much as whether the drug is investigational and how you would feel about that drug.

DR. CHESNEY: Thank you. Would that be a general consensus that this is an "it depends" answer?

DR. FOST: I want to give a concrete example of how it depends. If you had an infant with hips arrhythmia, with myoclonic seizures, for which there is no effective treatment, he or she, if he understood what was going on, might agree to a lot of inconvenience for a non-therapeutic study, for a PK study for a new drug that offered some prospect of that, so I would tolerate a lot of non-therapeutic studies in that situation as compared with the kid with his first onset seizure for whom maybe--it will always depend.

The main reason for saying this is not to sound like two-handed ethicists, but it is to head off the idea of algorithms that are created by the FDA or at a central level that make it very difficult for local IRBs and investigators to make judgments on a case, because no algorithm will anticipate all these many variables.

I think all we are all saying is that all these variables are important and they should be weighed in, but how they all add up in any one case depends on the disease of that kid, what else is available, and a bunch of other things.

DR. CHESNEY: Thank you. The devil is in the

details and it depends.

DR. MURPHY: Joan, maybe it would help for me to clarify one thing, is that it is not the intent of FDA at the end of this meeting to usurp the role of IRBs. We have no intentions of trying to become the ethical moderators of these.

We are simply in the situation of having these come before us and seeking advice, so I do want that clear, and I will try to summarize what we plan to do with the data at the end.

DR. CHESNEY: Thank you.

Dr. Gorman, I need better peripheral vision here.

DR. GORMAN: Maybe I should just wave further to the side here.

I think the difference whether this was an investigational approved drug would make for me is how I would be willing to see it studied in children. If it was an approved drug in adults again, I might be willing to choose this as a primary therapy in children in a controlled study. If it was an investigational drug, I would only see it as an add-on, I mean a very concrete

difference in terms of risks and benefits to kids.

DR. CHESNEY: Thank you.

Can we move on to F? Any comments if the pharmacokinetic design required obtaining 500 blood samples, would you allow the study to proceed or place any restrictions on the study? Comments.

DR. CLAYTON: Joan, I wanted to go back to A, something that Norm has said, because I think it is an area that, well, I know I disagree, and I want to bring it forward, which is that he has been positing the notion that the role of the IRB is that they should make the decision that the child could make if the child were suddenly to reach a moment of lucidity from their two-year-old state and make an adult sort of decision.

I must say that that is sort of the substituted judgment model that was in the Seckewitz case, and although I think that there is some usefulness that can be gained from that sort of analysis, I would really hesitate to rely on that, because I think it gives us a little bit more comfort than we actually ought to have.

I mean I think what we really need to be doing here is saying that we recognize that everybody here is

in a compromised position, that the parents are, the kid is, the investigator is, and that we at some level need to just face up to the compromised decision and just be clear about the tradeoffs that we are making.

So, I would be really hesitant to adopt Norm's model. So, I just want to give a dissenting voice since he has made that comment a couple of times here.

DR. CHESNEY: Thank you, Ellen.

DR. WILFOND: Can I add to that dissent, but also maybe a way of clarification because I think that Norm's intention is good, but I agree with Ellen that that may not be the best approach.

I think the point that Norm is really trying to get at with that notion of the substituted judgment, I think can really be translated to a best interests statement. In other words, we think this is really important research. I think that is what he is really getting at when he thinks that the child may make that decision.

I guess since I have the floor, I want to again re-register my own dissent towards the notion of there being a distinction between the healthy children versus

the children with the disease.

It is not clear to me if this is non-beneficial research, that there is any clear advantage to doing this only on children who have the disease if it is not going to benefit them. I guess I would be curious to hear somebody try to convince me that I am wrong.

DR. CHESNEY: If I can have the floor. To me, the benefit would be what Norm articulated, which is that you frequently do run out of medications because of side effects and the seizures become more resistant.

So, for the child with seizures, I can see easily where they could see a beneficial effect for themselves down the road, whereas, for a healthy child without a seizure disorder, there is no conceivable benefit for them is the way I would look at it.

DR. KODISH: I think the other thing that people have argued, Ben, and I think this is interesting speculation, is that there is this concept of a community of disease.

The kids with leukemia find altruism toward other kids with leukemia, more special in some way. Kids with asthma feel like they owe more to other kids with

asthma, and that is sort of the other side of the argument that you could make.

I share your reservations, though.

DR. FINK: Aren't we being a little presumptive, though, when we say that you are going to take young children who have a known disorder and disallow other children who are young, but may be at risk for developing the disorder. So, would you disallow a child to participate in this at age two, whose mother has a seizure disorder that requires chronic medication?

DR. CHESNEY: Well, let me argue that you could say that we ought to--well, this is emotional--but we ought to allow normal healthy children to receive antileukemic drugs because they might develop leukemia in the future. That would be sort of the extreme.

DR. FINK: It is a matter of probabilities.

DR. CHESNEY: It depends.

DR. GORMAN: I would argue that the siblings of people with seizure disorders might be a healthy population that would have altruistic motives to participate in these studies and might be considered as candidates, healthy candidates.

DR. CHESNEY: Thank you. That is a good point.

Dr. Spielberg, could you comment on this number of samples and your concept of putting in one access device, and how much blood, and so on?

DR. SPIELBERG: I think there are three things involved here. One is to really be able to justify the number of points on a curve that are needed to define the particular therapeutic endpoint, be it area under the curve, Cmax, Cmin. Very often adult pharmacokinetic studies involve 17 points on a curve. It is very elegant and it is often completely unnecessary either in adults or, for that matter, in children.

If we understand the PK in adults pretty well, one way of avoiding this is statistical approaches to selecting those time points that give you the most information, the most data, and even doing a population area under the curve, for example, three points at different times in different children, assembling that into a population curve, which avoids the necessity for multiple sampling.

The second point is there are guidelines from NIH on maximum volumes of blood that can be obtained for

non-therapeutic purposes. So, that is the second thing that an IRB is going to have to make sure of, and that a company, in planning the studies, is going to have to be sure of, but that also has to take into account not only blood samples that are taken for PK, but blood samples that are taken, for example, for a safety evaluation, liver function tests, and all these other things, and that has to be done a pediatric reference laboratory that will minimize the volume of blood.

The third thing is these days we should really be able to do the vast majority of blood sampling through an intravenous catheter, placed skillfully by somebody who does this all the time and knows how to do it.

But catheters also clog, and one of the responsibilities we have, both an investigators and IRBs, is to determine whether or not a second venipuncture would be offered to the child, and if the child says no, that is the end of it, and how many times that might be offered.

So, we have to think about those things up-front, and in study design, recognize that we are not always going to get perfect data out of each child, and

again, we are going to have to assemble information across many children to do what we would normally do in a smaller number of adults.

But the IRBs do have to determine whether or not it will be acceptable to do a second stick or a third stick, and what will happen if the child says no.

DR. SANTANA: Another possibility is that you could do an extensive PK study in a limited number of patients, look at that data, and then decide how many more samples are really appropriate for the population at large.

So, if you don't have enough data from adults that can guide you, you can do these six samples or seven samples in X number of patients, and then move on forward by knowing what the data looks like.

DR. SPIELBERG: Absolutely. I think all of these things have to be viewed in an iterative sense, and, in fact, if you are getting data that suggests to you that really clearance is pretty comparable in adults and in kids, you can drop back to a therapeutic mode and just do pop-PK sampling during the course of a therapeutic trial and cut the number of patients, which

again is the obligation in all of these situations to be looking at the data in an iterative way to minimize the amount, the number of patients studied, and minimize the burden.

DR. CHESNEY: Keith, you had a comment, and then maybe we can come to a consensus on this.

DR. RODVOLD: I agree with Dr. Santana because you can't do population analysis until you know what the model is. So, you can't jump there. So, you are going to have to do some kids to get or someone to get more extensive sampling, whether or not this is too extensive or not is up for debate.

The other complication, though, here is that in anticonvulsants, if this is an add-on, they usually have other anticonvulsants on-board, and also you have all kinds of dosage formulations where you could get into dumping syndromes and miss troughs when troughs were logically there, and so you are going to have to do some extensive sampling someplace along the line, and then riddle out drug-drug interactions in here, which is extensive in this area.

So, you come back to some of the questions

before the F, what population, other diseases, other drugs, lots of other things that make this question a little bit more difficult to answer.

MS. KORNETSKY: I will be quick. The other thing that I just wanted to point out in looking at this time period, this appears to me that a child would have to be admitted for a 24-hour period, and I haven't heard any discussion, but I think that also needs to be taken into consideration, not just the physical risk, but the risk of someone who may not require hospital admission for purposes of the research.

DR. CHESNEY: Thank you.

DR. WARD: Depending on what we know about metabolic pathways in adults, we may have to study kids at different stages of development, and so this may not be appropriate to try to determine this population PK in only one set of individuals.

DR. CHESNEY: It sounds to me like this would also be an "it depends" answer. Is that fair?

DR. SPIELBERG: It depends, but the science is there to be able to guide you.

DR. CHESNEY: Right, depending on the

circumstances, we do have the science to give us the answer.

DR. SPIELBERG: Exactly, and we shouldn't be talked into either too many samples or too few samples. We should get the right number to get the data.

DR. CHESNEY: Thank you.

Moving on to G. Just to remind you, if we are now using an antihistamine instead of an anticonvulsant, given orally, already been approved for use in adults, to asymptomatic healthy children, single dose of the antihistamine, obtain one or two blood samples for a PK study.

Going back over A through F, does this study with an antihistamine that has already been well studied in adults and approved for use, when we have to obtain at least one blood sample from the child assuming we put in a catheter and can get two samples, does this study exceed the threshold of a minor increase over minimal risk?

Comments. Dr. Nelson.

DR. NELSON: I will go out on a limb and say it would change my answers dramatically on every single

point, and most likely I would consider it acceptable under minimal risk with the exception of F, which I would need some further thought on in how to carry that out.

DR. CHESNEY: Dr. Kauffman.

DR. KAUFFMAN: I would like to respectfully disagree because I think that physician assumes that the benefits and risks of the antihistamine are dramatically different from the anticonvulsant, and without knowing more about the drug, I don't think we can say that.

We are assuming that it would be given for a trivial condition, and we are assuming that antihistamines are generally very, very safe drugs when we say that, and we know differently, so I would disagree and treat it the same as the anticonvulsant.

DR. NELSON: I guess I was assuming if it were approved, that much of that information was available.

DR. KAUFFMAN: If it was seldane, and they got an arrhythmia, it is not safer.

DR. CHESNEY: Other comments? Keith.

DR. RODVOLD: I agree, I disagree because I think more of the newer antihistamines have been metabolized, and so you have to go back and you have got

to look at some things that even if it was approved in adults, that you have got to be careful and going backwards and take a look at adverse events and metabolism and pathways, and other drugs that--you know, if it's in volunteers and they won't be on drugs, or if you are going to take someone that is on drugs. So, I think you have got to back up again.

DR. NELSON: Let me try to make a stronger case.

This is an approved medication, and we know that pediatricians, being one, and there is pediatricians around here, basically go wild once it's on the shelf and prescribe it for all sorts of indications off-label.

So, in effect, we have got a situation here where we would not allow healthy children, which are the ones that are likely going to be getting the antihistamine by their pediatricians, to not go into a research project out of these concerns when it is going to be used in hundreds of thousands of children once it's off label.

So, I agree with all the concerns about safety and those need to be addressed, but to me this begins to fit into the minimal risk category, and the argument

about exposure, and even if it's minor increase over minimal risk. If you argue this is greater than a minor increase over minimal risk, this just wouldn't happen, it wouldn't get done, IRBs wouldn't approve it.

I agree with the safety concerns, but to me, this is a population that would need to get this medication because that is the group that would be getting it.

DR. CHESNEY: Excellent point.

Dr. Edwards.

DR. EDWARDS: It seems that we have kind of gone back to the first case in a way. I mean it's like the antibiotic case, I think, and obviously, some of the cardiac toxicity that has been reported with some of the antihistamines would be another issue, but I think it is more back to the first model, I would concur.

DR. CHESNEY: I think the only difference is that in this case, the child has to have a catheter or two separate venipunctures.

DR. WILFOND: I realize in listening to the conversation that one of the problems with Question A, the way it is stated by focusing on the minor increase

over minimal risk, really does tie all of our discussion to the specifics of the regulations.

I think the more general question that we ought to be asking is do we think this sort of study is justified in healthy children rather than tying it to other what we label as minimal risk or greater increase in minimal risk, and in that case, I would say that if we had reasonable information about safety, whether it is for an anticonvulsant or for an antihistamine, I think we might be able to say a PK study might be justified in children, and that is regardless of whether they have the disease or not.

DR. CHESNEY: I am reminded that we are already way behind.

I would be interested in an actual show of hands for the answer to A, and let me put it this way. How many people would agree with Dr. Nelson's perspective as he presented in two different comments?

[Show of hands.]

DR. CHESNEY: Seven.

How many would agree with Dr. Kauffman as presented in one comment?

[Show of hands.]

DR. CHESNEY: Two. Thank you.

B. Would any precautions or exclusions minimize the risk that you feel is present?

Dr. Kauffman.

DR. KAUFFMAN: Well, I think if I knew from adult data, from adult experience, that this had a very good safety profile, then, I would view this essentially as being minimal risk. I agree with Skip that we have to weigh into this, we have to factor into this whole issue what is the risk of not doing the study, because that is really the issue that he raised, and that has to go with all of these examples, and I totally agree with that.

As long as I could be assured that the safety profile in adults was acceptable either in if it is not approved, in the preapproval studies in adults, or if it is approved, it is even stronger, then, I would view this as a minimal risk.

DR. CHESNEY: Thank you.

Maybe we can go to C then. Could this study be given in children who are too young to give assent? Can we give an antihistamine in this setting to a

two-year-old? Comment? Yes.

DR. SZEFLER: It should be yes, and just to follow up what Ralph had said, most of the arrhythmias are on multiple dosing regimens, and it's the context of the study and the study design, and this is just single-dose studies. So, I don't see an excessive safety feature here, knowing the profile of the drug unless there was something very unusual.

DR. CHESNEY: Does anybody disagree that this could be given to children who cannot assent? Dr. Nelson.

DR. NELSON: I just want to give one plea. As you recall, one of the early principles that were put up in our presentations was that participants who could consent should be used preferentially over participants who could not consent.

The question I have is why we would not apply that same principle in a descending age range, which I believe was raised by Ellen, to pediatric studies, and although I would have no objection to including children at some point who could not assent, unless there is good developmental reasons metabolically or otherwise that the

research needs to be done in that population, I would want to see it moved down the age range--you can move down fairly rapidly--but move down the age range before that is instituted.

DR. CHESNEY: Thank you. Good point.

D. Would it make a difference if the child had I assume a disease which required antihistamine? I don't know exactly what that would be, maybe urticaria. I think we have agreed that we are happy studying this in well children who don't have the disease.

Would it make a difference if this antihistamine had not been approved in adults and we had only minimal to moderate information about the kinetics and adverse effects, and so on? Yes, Dr. Danford.

DR. DANFORD: I will venture a statement that maybe it would particularly with the concerns we might have about arrhythmias, et cetera, in some antihistamines that we may learn about relatively late in our experience with them.

DR. CHESNEY: Does anybody feel strongly that we would not approve of this if it was an investigational antihistamine?

DR. WARD: It's all about what Steve said earlier. It all depends upon the details about the pharmacology of the drug itself, and most of the drugs are now being screened for effects upon the IKR channel as they come through the development process. So, we would know that in advance.

DR. SPIELBERG: And it is not antihistamines per se that are involved in that. It is the nature of the molecule and hitting the IKR channel, and it has very little to do with indication, they are antibiotics, that also prolong QT, including our friend erythromycin.

Just to very quickly pick up on something, though, that Skip said, and I didn't say this with respect to the number of samples and everything. The issue of doing, if you will, the more difficult studies in the older kids, knowledge of PK and everything, so that the little kids don't, in fact, have as great a burden for doing the multiple sampling.

If you have enough information about metabolic pathways, if you are smart enough in study design, you can spare the youngest children the requirement for multiple sampling and go to a more loose population

design in the context of a clinical trial to maximize their benefit, so again, just thinking along those issues.

DR. CLAYTON: The only point that I was going to make here is that as I look at this, I realized one of the reasons that the antihistamine example is on here is that we mostly think of that as being a relatively trivial disease and also drugs that are used like water, and they certainly are, and actually usually have the efficacy of water at least in the small child.

But I do want to make the point here that there are at least some small children for whom antihistamines make a huge difference, and there is actually really life-threatening disease that fits in this category.

So, I just want to sort of throw that little caveat in there, because I know part of the antihistamine thing is that, you know, mom and dad are tired of listening to little Johnny snuffle, I mean really tired, but there is actually a subpopulation of kids for whom this really makes a big difference.

DR. GORMAN: I feel less comfortable doing this as an investigational drug for antihistamines than

anticonvulsants, because I think the therapeutic options are more varied and more effective for the antihistamine class, and would change my answer for the anticonvulsants where this would be okay, to the antihistamines, as I said, I would want to see adult approval or at least the Phase III studies in adults complete.

DR. CHESNEY: Thank you. Actually, I am not sure what the consensus on E is. Could somebody else articulate?

DR. SPIELBERG: It depends.

DR. CHESNEY: It depends. Thank you.

We said F was it depends if it is an anticonvulsant. Do we hold with that if it is an antihistamine? Yes.

Case Study No. 3

DR. CHESNEY: Moving on Question No. 3, which we should be able to get through in 15 to 20 minutes.

A sponsor has developed a new formulation of an ophthalmic agent, which is approved for use in adults. The study population is to be asymptomatic, healthy children of 3 through 8 years. The design is to provide each child with a single dose in the eye, observe for two

hours for adverse events, and if none are noted, then move to a 6-week multi-dose study. It is not known if such agents would have any unique impact on acuity in this age group where visual acuity is still developing.

Question A. Does this study exceed the threshold of a minor increase over minimal risk?

Let me start again by asking what people would interpret as the risks of this 6-week, multi-dose study.

Yes, Dr. Edwards.

DR. EDWARDS: I don't think we are given enough information about this ophthalmic agent. Is it an antibiotic?

DR. MURPHY: No. We have a pediatric ophthalmologist, Dr. Wiley Chambers, who is the Division Director, who I think can give us--we thought this might get your attention--some clarification to really where we see these studies occurring and why they are being done.

DR. CHAMBERS: My name is Wiley Chambers.

The context for these are these would be virtually all antihistamines or mast cell inhibitors. They would be studied for their safety and efficacy in a population that went from approximately age 8 through age

99.

The studies would normally be conducted in that age range because we are looking for both--the indication would be allergic conjunctivitis--and so we are looking for the ability to get rid of itching and the ability to get rid of redness.

We do not generally feel that people under the age of 8 are capable of giving reliable answers for the itching, but there is no reason to believe that the disease is any different between age 8 and age 99.

So, the initial safety and efficacy studies are done there. The disease we believe exists down between ages 3 and 8, probably not any different. We just cannot get the answers for itching below that age.

The eye normally does not finish its development and hence the risk for amblyopia and the risk for minor irritations exists between ages 3 and 8. Consequently, the proposal would be to do a study in subjects age 3 to 8 as described.

DR. CHESNEY: Dr. Gorman.

DR. GORMAN: Two questions. One, why would there be a new formulation, are children's eyes between

ages 3 and 8 different on the outside than children between 8 and 99?

Secondly, discussing visual acuity as it is developing in this age, would the ophthalmologists elucidate whether they think that is glove, lens, cornea, or is it really all brain development that is impacting on visual acuity development during that time?

DR. CHAMBERS: Maybe a new formulation was a poor choice. I mean this would be the same formulation as what was studied between ages 8 and 99, the exact same product. We are just looking at the potential risks between ages 3 and 8.

The exam would not include just visual acuity. We also include slit lamp exam, so that we could determine if there were any abnormalities--both look at the cornea conjunctiva--and look at whether there are any abnormalities and source of what the visual acuity difference would be if one was found.

DR. GORMAN: But does visual acuity change in this age because of differences, development in the lenses--yes or no, that is true--or development in the brain? I guess that is the question I am trying to ask.

What impact are they looking for?

DR. CHAMBERS: The general feeling is there is not a full development of the retina. The risk for amblyopia is both a retinal, as well as optic nerve going to the brain. The exact pathway is not entirely well know.

DR. SANTANA: So, in order to get this data, you would have to EUAs on these kids, exams under anesthesia?

DR. CHAMBERS: No.

DR. SANTANA: I don't see how you can do all these things that you keep talking about - retinal exam and slit lamp, you know, it is very difficult in 3-year-olds to do all these things.

DR. CHAMBERS: I would beg to differ. It is not particularly difficult to do a slit lamp exam. There are things called hand-held slit lamps. We routinely examine children age 3 and above. It is not a difficult exam. We are not doing any special tests for these. We are not talking about visual evoked potentials, we are not talking about ERGs. We are talking about basic typical tests that would be done in any kind of normal exam.

DR. WILFOND: It sounds like the main concern

for including children of this age is because of this concern about impact on visual acuity.

Have there been other drugs previously where that impact has been identified?

DR. CHAMBERS: The difficulty in essentially why do this at all or why not do it in people that have the disease is that if you were to take children that have the disease, their eyes would typically be red and itchy, which are some of the early warning signs or early signals if you had some minor irritation due to the drug product. So, you wouldn't be able to differentiate whether the drug was doing the same things as the disease typically manifests. That is the reason for doing it in normals.

Visual acuity is just one of several tests that would be done.

DR. CHESNEY: Dr. Nelson.

DR. NELSON: I guess if one of the justifications for extrapolating efficacy data is the similarity of the disease, and if there is no postulated difference in the reaction to local irritation, it strikes me given the nature of the risks that you are

worried about, those risks in my mind could only be justified if there was potential benefit.

So, I would argue that it should be the population of children with allergic difficulties who would be the population to assume that that wouldn't be a safety endpoint that necessarily needs to be determined, because that has already been sorted out in 8-year-olds, because the reality is pediatricians are probably using this anyway if it is already approved.

I am really struggling and since it is not part of A, B, C, or D in terms of your patient population, I would argue that it should not be used given the nature of the risks you are precisely worried about following in someone who would not normally be exposed to this medication, and then just ignore the fact that you can't collect that particular safety data given the allergic reaction.

DR. CHAMBERS: The risks for irritation are potentially different.

DR. NELSON: I understand, but you are assuming the reason why you are extending it to the 3 to 8 population is because of the issue of visual acuity.

DR. CHAMBERS: That is one of the issues, it is not the only issue.

DR. NELSON: Understood, that is one of the issues, but I would argue there is no reason to assume that a 7-year-old would have any more propensity to local allergic reactions than an 8-year-old.

The problem I have in this--and it's not A, B, C, or D--is I would not give this to asymptomatic healthy children after what you just told me about the risks you are worried about and that you are going to follow for.

I, as a parent, wouldn't even put my kid in, I am not sure I would put my own eyes under this from what you have just described.

DR. CHESNEY: Dr. Edwards.

DR. EDWARDS: Are there any data that could be derived from animals, looking at acuity and issues with chronic use of this medication, particularly the concern that you have?

DR. CHAMBERS: No.

DR. CHESNEY: Dr. Fink.

DR. FINK: I guess I would raise the question, one, I think this is increase over minimal risk, but

secondly, is there any data--I would want to see some data to support that there was actually a market for this drug. Usually, allergic conjunctivitis in the 3- to 8-year-old is going to be more effectively treated with systemic antihistamines, and as a parent, I can't imagine long term trying to fight with my child to give eye drops day after day.

DR. CHAMBERS: For itching and redness, the most effective products are actually the eye drops. They are not the systemic. Head-to-head comparisons that have been done have demonstrated this. The market is relatively large. What we are talking about is the development of virtually every ophthalmic allergic conjunctivitis product that has already been on the market and continues to be on the market. This is not a single, one-time thing. This is the routine.

DR. CHESNEY: Dr. Clayton.

DR. CLAYTON: Actually, I was going to follow up on that say that I am not even sure, as a pediatrician, that if a parent asked me if they should be putting this stuff in their kid's eyes, that I would say, you know, that I would encourage them to go through the battle of

putting this stuff in their kid's eyes as opposed to just letting them have red, itchy eyes.

Even if systemic antihistamines would be less effective, if the kid tolerated them well and the kid took the oral antihistamine well, I think that I would prefer that. I mean I don't know. I mean it is interesting to hear that there is a potential market out there, because I am not sure, as a pediatrician, that I would recommend that a parent do this.

DR. CHESNEY: Other comments?

DR. CHAMBERS: I would be interested in hearing if it's above minimal risk, what are the risks.

DR. LUBAN: Application of the drops alone. I mean holding the eye open and putting in drops in a 3-year-old would just--fighting, getting scratches on the cornea from the application, and then the slit lamp puts it into an entirely different ballpark as far as I am concerned. Then, you are talking about dilation.

DR. CHAMBERS: The slit lamp does not require dilation. The slit lamp does not require contact. The slit lamp, you are talking about being a couple feet away from the child to do the exam.

DR. LUBAN: As I remember, don't you have to have the head stable?

DR. CHAMBERS: Not with a hand-held slit lamp, no. DR. CHESNEY: Ben.

DR. WILFOND: I just want to respond real quickly to Wiley's question about risk. I think earlier today we were using the word risk very broadly to talk about discomfort and inconvenience, as well as physical harm. I think the concern would be to what extent, again, does the application cause discomfort or unpleasantness.

DR. CHESNEY: Dr. Spielberg.

DR. SPIELBERG: I am really worried about--let's say the stuff really did work--I am terribly worried about compliance under such circumstances. I mean if your average Hopkins' house officer never finishes a 10-day course of antibiotics for their own kids' otitis, despite what they tell their parents to do, this is six weeks' worth of eye drops in a child.

I mean most parents will give up after two or three failures with oral medicines. That is sort of standard routine. Here, you are asking somebody to do

something really pretty extraordinary. Even in treating bacterial conjunctivitis, it is hard for the parents to put drops in for even a week. Six weeks, in honesty, I think will become a major home battle, and a major home battle for a 3-year-old is distressing and risk.

DR. CHAMBERS: Wouldn't that be worth knowing before the product was approved? Is that not something that you would want to know before the product was indicated for that age group?

DR. SPIELBERG: I would want to know it. In honesty, I think I would, and probably be developing it for that group after I talked to a bunch of moms.

DR. CHESNEY: Dr. Nelson.

DR. NELSON: In my mind, the most worrisome risk is the one you identified in your last sentence, which is what you really don't know whether it would or would not happen, which is the visual acuity, and I would ask a question.

Assuming these are available by prescription only at this point for those other populations, and given the propensity of pediatricians to do off label use, whether you would be able to even get some preliminary

information about the frequency of use in this age group and whether you would be able to assuage those of us who would be worried about impact on visual acuity just by looking at those children who are already receiving this medication.

DR. CHESNEY: In the interests of moving ahead, can I ask, is the consensus that people feel that this situation does represent more than a minor increase over minimal risk? Yes.

DR. MURPHY: Joan, instead of going through all the others, then, could you pose another question. Would you consider it appropriate to study this age group with this agent with all the information you have heard if there were a history of the child having had this problem before?

DR. CHESNEY: Ben.

DR. WILFOND: I don't want to just keep repeating myself, but again, I would say I don't think that would make much difference because I think that the risk to the child and discomfort are going to be to a large extent independent of whether the child has had a previous episode of conjunctivitis.

DR. CHESNEY: Dr. Gorman.

DR. GORMAN: I think one of the issues may be the age range we are picking, going down to age 3 and having the oppositional battles at that age.

There are clearly some 5-year-olds who would tolerate eye drops without any difficulty, and after a widely used mast cell stabilizer was withdrawn from the market because they had difficulties in manufacturing, I had several parents drive to a country that is on the other side of the border to get this agent and bring it back for their children.

So, I am going to have to respectfully disagree with those that think that it is always a battle to give eye drops, and I know that there is a subset of our patients who really object to systemic antihistamines on a chronic basis, which has been offered as an alternative, as well.

So, I think maybe it is the age range down to 3 that is problematic more than some of the other concerns that we had, because I think that battle is a problem.

DR. CHESNEY: Yes, Keith.

DR. RODVOLD: I think it would help if you had

some type of model even if there isn't one, because you are saying acuity is still developing, and to give humans that at this point, especially in kids, that is really worrisome to me. You have a big safety unknown sitting there.

If there is no model, then, develop it. That would kind of help assure some of this, or multiple models. That may take over one hurdle of a safety issue that is reluctant, but you still come back to the practical issues of convincing parents and people that do this for such a long period of six weeks, maybe a shorter period initially, and then go on from there.

DR. CHESNEY: Any further comments on Case No. 3?

Dr. Murphy, can we take a 15-minute break now?

DR. MURPHY: Please.

[Break.]

DR. CHESNEY: Before we get to Question No. 4, Dr. Chambers wanted to clarify one of the issues that was brought up in the Question No. 3 about a topical ophthalmic agent.

DR. CHAMBERS: Just for clarification for

informational purposes for people, the antihistamines and mast cell inhibitors from the ophthalmic perspective, this has been the routine for the last approximately 10 years.

There are probably 10 products that are antihistamine mast cell inhibitors which have been studied in 3- to 8-year-olds, normal individuals for six-week studies, given four times a day. There have been no safety problems in any of the studies. The compliance rate generally runs somewhere between 95 and 99 percent of people taking the medications, following through, following the questionnaires.

We do occasionally get people that don't like taking the drops, and we find that out within the studies. This has been the routine that has gone on. There may have been also some misunderstanding about--these products don't have an increased risk of altering visual acuity. Antihistamines mast cell inhibitors, to our knowledge, don't do anything to visual acuity. It's that the eye has not finished developing until the age of 9. It's not that there is any special risk with these products as opposed to any other product.

It's just the eye hasn't completed its development, and that's why we generally ask for studies in the lower age groups, and we ask for studies for all ophthalmic products, as low as the age goes. For allergic conjunctivitis, we ask for down to age 3, for neonatal conjunctivitis, we go down to within hours after birth.

DR. CHESNEY: How do you measure compliance?

DR. CHAMBERS: It's a questionnaire that is done by the parents.

DR. CHESNEY: Do you offer an incentive?

DR. CHAMBERS: Most of these trials do have a monetary incentive, yes.

DR. WALTERS: How often a day and for how many weeks do the people 8 and above take the drops?

DR. CHAMBERS: The different products are indicated different frequencies. The most frequent is four times a day, the least frequent is twice a day.

DR. WALTERS: And for how many weeks?

DR. CHAMBERS: We generally try, since most allergy seasons tend to run somewhere between 6 and 10 weeks, all these studies all go for a minimum of 6 weeks.

DR. WALTERS: And a maximum of?

DR. CHAMBERS: If we say a minimum of 6 weeks, every company runs it for 6 weeks.

DR. CHESNEY: Have you studies visual acuity in these children? I think that was somewhat confusing to all of us. It implied that it wasn't known.

DR. CHAMBERS: Visual acuity is monitored along--there is generally, for a 6-week trial, there is the initial visit, there is usually a visit either day one or week one, but relatively early on, there is usually one halfway between, and then at the end, and visual acuity is measured by the ophthalmologist at that time.

Depending on what the development is, visual acuity is measured in different ways and for younger children, it is whether the eyes are center steady maintained. We are not talking about necessarily eye charts. As you get old enough to be able to read eye charts, then, we do that, but it is age-appropriate visual acuity.

There is usually some type of slit lamp exam, and there is an external exam, and that is basically all

that is generally--and the questionnaire.

DR. CHESNEY: Are there questions and comment of Dr. Chambers? Yes.

DR. O'FALLON: The real issue is long term, it seems to me, in this visual acuity. Have you guys ever done any follow-up studies a couple of years down the line to see what is happening especially, or do you ever do studies, randomized studies, in which there are different things, and you look to see whether the acuity affected long term?

DR. CHAMBERS: To my knowledge, there has not been anything done long term. As I said, the products don't have a risk at visual acuity, it is just the eye has not developed. These are all randomized trials.

I mean this is not just everybody receiving the antihistamine. This is a two-to-one randomization with twice as many people receiving the antihistamine or mast cell inhibitor and one-third of the people receiving vehicle.

DR. O'FALLON: It sounds to me, though, that a long-term follow up would give you more information ultimately on whether there is a visual problem.

DR. CHAMBERS: I will take that into consideration. Thank you for the comment.

DR. CHESNEY: Thank you.

DR. CHAMBERS: Thank you.

Case Study No. 4

DR. CHESNEY: Question No. 4. A sponsor is developing a new MRI contrast agent and wishes to test safety and tolerance in children. The study design is to give one dose of the intravenous contrast agent to hospitalized children who already have indwelling catheters, or who have previously established intravenous access, and to observe the children for reactions for two hours.

The first question. Does this study exceed the threshold of a minor increase over minimal risk? Maybe we could start again with clarifying what the risks of this particular study are.

Comments?

DR. GORMAN: Has it been studied in adults yet?

DR. MURPHY: We will say for this, yes.

DR. GORMAN: One more clarification on the study. Is this child coming in for an MRI or is this

child just in the hospital?

DR. MURPHY: I am trying to think back to the actual study. The child was just coming into the hospital and had a line in.

DR. CHESNEY: Was not being admitted for the MRI study, though, was being admitted for other reasons?

DR. MURPHY: Correct.

DR. CHESNEY: Dr. Fost.

DR. FOST: So, it has been shown to be safe and effective in adults, I assume, for the sake of discussion.

DR. MURPHY: For the sake of discussion.

DR. FOST: If that is the case, why would you not want to use children who have some potential benefit, that is, children for whom an MRI is indicated?

DR. MURPHY: You may wish to.

DR. FOST: I would wish to.

DR. CHESNEY: Any other comments? What are the risks of this?

DR. KAUFFMAN: I don't know what the risks are. There isn't enough information here to know what the risks are. They could be tremendous, they could be

trivial. I don't think we have enough to answer that question.

Some of the radiopaque materials in the past have had major risks, and so I don't know what we are dealing with here, but I agree with Dr. Fost that I don't see any reason why this study should be designed the way it is portrayed here.

There is no reason, if you want to evaluate this material, it not be used in kids who are getting MRIs because we have thousands of them, tens of thousands of them every year that are getting MRIs with contrast. Just look at the tolerability in that population. Why place normal children at any additional risk if there is any.

DR. CHESNEY: Dr. Danford.

DR. DANFORD: You asked for risks. One of the risks I can think of is some contrast agents are thrombogenic. You would hate to take somebody who has a central venous line for a very good reason and make that central venous line of no further use to the patient, this, on top of the usual hazards of entering a central venous line including infection and the risks of the

agent itself, idiosyncratic allergic reactions, et cetera.

DR. CHESNEY: Thank you.

Dr. Clayton.

DR. CLAYTON: I would just make another comment here, which is that--again, this relates to my particular experience dealing really only primarily with underprivileged children--and that is, that many of these families perceive coming into the hospital and perceive dealing with house staff and residents and students as being experimented on, and so I think when you have got a child who is in for another reason, maybe they have got pneumonia that is unresponsive to therapy or whatever that is, that, you know, you really need to be careful about asking those families to do something else unless it is something that is particularly related to them.

I think that in a society like ours, where a substantial part of the population profoundly distrusts us, and profoundly fears research, I mean yes, we are asking them, and I think all of that is important, but I think in addition to that, that is yet another reason why to take a child who is already sick and even if the

contrast agent seems to be relatively safe, I think you have to have a really good reason why you are taking this particular patient population and asking them to do an additional thing, and I think we have to be attentive to that history.

DR. CHESNEY: Dr. Nelson.

DR. NELSON: Just to reiterate the problem I think of standards, as we have discovered, the whole interpretation of minimal risk is problematic and one of the difficult issues is whether you index that minimal risk to the life of a healthy child or to the life of a sick child.

In the original National Commission's report, it was indexed to a life of a healthy child, and then Subpart D or I should say the Common Rule, for some reason, dropped out the phrase "of healthy children." So, it opens up an ambiguity.

Now, the OPRR's official position is they would like it to be indexed to healthy children, but in fairness, you could interpret the regulations liberally on that point.

So, my only plea is if we are trying to develop

regulatory language or guidance over time, is that we don't get into a situation where we are debating whether minimal risk means the same thing as low risk or minor increase is the same thing as low risk, but at least we are debating what the language itself actually means as to whether or not minimal risk is a certain situation, because otherwise we just compound the interpretation difficulties.

DR. WILFOND: I actually want to get back to Ellen's point. I agree with her, but would actually add some additional reasons why I think that this may be problematic to do in this group of children.

Those are, first, I think there is always the potential for there to be some confusion, that, in fact, that this study is therapeutic in spite of the fact that there will be disclaimers that it is not, precisely because the kids are in the hospital setting presumably to get some treatment.

Related to that, there would be the concern that given their situation, they may be concerned that they are not really free to say no in spite of our disclaimers that this is not the case. I think those things are

minimized by taking children who are not already in a compromised situation being sick.

DR. CHESNEY: Dr. Gorman.

DR. GORMAN: I think this is one of those cases where we are going to expose a fair number of healthy children. At least in my institution, a fair percentage of the MRIs done for therapeutic indications are, in fact, normal. So, they will have a therapeutic indication, but they will still be healthy at the end of their MRI.

DR. CHESNEY: Are we in consensus that for a child who would not otherwise receive MRI dye, that this does exceed the threshold of a minor increase over minimal risk?

Yes.

Are there are precautions or exclusions that you feel would minimize the risk in an otherwise healthy child?

DR. NELSON: I don't want to delay us too much, but my impression of our answer to Question A was that we can't answer whether we think it is minimal risk or not because we lack the data.

Part of the difficulty is, you know, I think the argument that it ought to be applied to children with that condition is really independent of the risk argument.

DR. CHESNEY: Let's go back to the question of whether we do think that getting a child hospitalized for another reason--and we don't know what that is--it could be renal failure, hemolytic uremic syndrome, presumably people would be cognizant of that issue, does giving a dye represent more than a minor increase over minimal risk?

DR. FOST: Is the idea here that they are just going to get it injected, they are not going to be scanned, is that the idea?

DR. CHESNEY: Correct.

DR. EDWARDS: How are they going to know it's a better contrast if you don't look at it? I mean they are going to have to have a procedure. I mean you can't just inject it to make sure, I would think.

DR. MURPHY: This is for safety.

DR. NELSON: I guess I just want us to keep the issues clear. I mean risk is defined as probability and

magnitude of harm. If we don't have the data to make any judgment of probability and magnitude of harm, that is one issue. The other issue is whether it is justified if we had that data to do it in a population that is having an MRI. That is an entirely separate question.

I would ask us to keep them clear and separate. If we are saying we don't have the data to judge risk, we should stop there, and not try to then link whether we do it in the child with or without a condition for an MRI, then, to the presence or absence of that data. It is a separate question.

DR. CHESNEY: Thank you for clarifying that.

What additional data would you want to assess risk?

DR. KAUFFMAN: I think we can't make the mistake of thinking about risk in isolation from benefit. Somebody made that point earlier today. If you write the equation risk/benefit equals something, and benefit, as it is in this case, zero, then, risk is infinite even if it's minimal.

So, I think that is how we have to look at this particular study, and so we need to know more. That is

why I say I don't think you could do this study unless you are doing it in the context of doing an MRI because then, at least there is some possibility, even in the child who may turn out to be normal, as Rich says, at least they receive the material with the anticipation of some benefit from the study that was done, but to do this the way it is designed, I just can't see any rationale for it.

DR. FOST: Ralph, I think that is a road you don't want to go down, about risk-benefit ratio being infinity when there is no benefit, because that would prohibit you from doing a single venipuncture on a child with no conceivable benefit to that child, even a minuscule risk give you, if the denominator is zero, then, you have got infinity, so I don't think you mean that.

DR. CHESNEY: Ellen

DR. CLAYTON: I just want to say that I want to be clear actually what I was talking about as distinct from just the risk issue, which is that I think as we go through this topic, that we look not only at risk, but benefit and distributional issues, and frankly, the point

that I was making is that I would vastly prefer to do this study on healthy children as opposed to sick children who are otherwise in the hospital.

I think that that population is considerably more vulnerable and particularly among the population of patients whom I treat, there is an additional risk that is outside the research context that weighs very heavily on my mind.

So, you know, certainly I would prefer that we do this on a population of children who are going to get MRIs for which they would need contrast anyway, but second to that, my second patient population would be healthy kids, and I would think that I would want to avoid this particular population of patients a lot, because I think the risk of putting an IV catheter in a healthy child is less than the risk that I discussed with an otherwise sick child who is in the hospital.

DR. CHESNEY: Dr. Fink.

DR. FINK: I think part of it depends on your view of the contrast agent because MRI contrast agents are not dyes, they tend to be extremely safe, and one could make the argument that the biggest risk in this

study is actually the intravenous access, not administration of the contrast agent, in which case you then justify using patients where the access is already available because it minimizes the risk of the study.

DR. CLAYTON: Oh, I understand that point. My point really had more to do with the context about whether the families would feel like they were being just further abused by a system that they already perceive is being abusive.

DR. CHESNEY: So, this is a very vulnerable group of patients.

DR. CLAYTON: Right.

DR. CHESNEY: Ben.

DR. WILFOND: I would agree with that last point, but in addition to that, I think that for a parent having to make a decision about whether to have their healthy child have the discomfort of intravenous access placed versus a sick child who already has access, who runs the risk of either losing that access or getting an infection, I think a parent would be more prudent to select the healthy child rather than a sick child for participation in the study.

DR. FOST: It is important for us to remember that not all the questions under each of these cases are being asked, that is, we are only being asked a handful of questions about risk in a sentence, but one of the questions presumably is it appropriate to do this study in this group on ethical grounds, and (b), is it consistent with the regs.

To pick up on Skip's point, even if you concluded that this was a minimal risk--and I agree with him we don't know at this point--if I am remembering just the rules, forget ethics for a minute, about studies of no benefit to the child, it has to be the case that it's information that can't be obtained in any other way or can't reasonably be obtained in any other way, that this can be obtained in another way, namely, by doing it on children who have an indication for an MRI.

So, I agree with Skip, the minimal risk thing is a necessary condition for approving this, but it is not a sufficient one. Even if it's minimal risk, I think almost everybody is saying they would have trouble approving this study, not because of the risk necessarily, but because it is not necessary to use

healthy children to get this information.

DR. MURPHY: Joan, I think when the answer is basically no, and a fairly clear no, that we don't have to work through every one of the questions if they are inappropriate to do that.

Actually, if there is some point, though, and I think the issue we were getting at with the hospitalized children, okay, if there is some point that this group wishes to bring forth in this discussion, that we have failed to try to outline here, I would ask that they bring it forth in this discussion.

DR. FOST: I am sorry, I didn't hear the first half of what you said.

DR. MURPHY: I was saying that if the answer is clear that in this situation, this population should not be a healthy population, and we don't need to work through all the subcategories. The subsequent questions were mostly we didn't want to presume a no answer, so if it's a yes, we have provided all the subsequent questions, but if it's a clear no, and there is not other way that you feel that the rest of these questions would apply, then, we don't need to work through them is what I

am saying.

DR. CHESNEY: Yes, Judith.

DR. O'FALLON: I am concerned about another issue here. If we say that really the best population is the kids that are facing the MRI, then, that strikes me as creating another issue, which is asking kids to forego a known effective in order to ascertain toxicities of a new agent, and I think that has got issues right there.

I mean, you know, by saying that is the population, I think that creates other problems.

DR. CHESNEY: And I think that gets back to Norm's point that there are a lot of questions that we weren't asked specifically.

DR. FOST: But that is true of any therapeutic trial, at least half the study population is always going to forego the standard treatment in exchange for something that might be better.

When I suggested--and I assume others did, but maybe it wasn't clear--doing this on children who need an MRI, I had in mind not just doing the safety study, that is, not just injecting stuff and saying have a nice day, but this should be combined with a child who has a

clinical need for an MRI in which you would give whatever the right dose was, because I assume the risk would be not immensely greater from giving whatever--that is, you are worried about sensitivity reactions, for example.

So, this seems to me is no different from any new therapeutic agent diagnostic in this case, that is reasonably tried when there is good adult data on children who have something to gain from it.

DR. FINK: What would be the ethical consideration if this were a new agent, well studied in adults, proven to be safe, no more effective than currently available agents, but a quarter of the cost, and now is to be studied in children?

DR. FOST: Well, that involves a whole set of questions. I mean FDA doesn't consider costs, I assume, in deciding whether or not to approve it, but cost is a relevant factor in patients deciding whether or not, depending who is paying, whether they are paying out of pocket, it might be very relevant.

I mean it would be a relevant factor in the consent. It would seem to me it is a good reason for doing the study if it looks like it is equally effective

and safe, that is a plausible reason for trying to use it in children, as well. It is in the interests of children, as well as adults, to lower health care costs.

DR. CHESNEY: Ellen.

DR. CLAYTON: It is also in the interests of children to have data since the less expensive one is the one that is likely to end up on the formulary, so it is the only one you can get.

DR. CHESNEY: I just want to be sure that we have a consensus as Dr. Murphy mentioned, using Dr. Nelson's clarification of the issue, in this vulnerable hospitalized patient population, are we in agreement that giving this contrast does exceed the threshold of a minor increase over minimal risk? Yes.

Okay. Then, let's go on to E. Assuming that this was not a hospitalized child with a line in, but rather a child admitted for PE tubes, who was to receive an investigational antibiotic prior to the surgery, and the middle ear fluid was sampled when the child was under general anesthesia, and although it doesn't say it, my assumption is that the serum sample would be obtained also while a child is sedated, does this study, the PE

tubes and an antibiotic, exceed the threshold of a minor increase over minimal risk?

Dr. Nelson.

DR. NELSON: Let reframe that. It is asking whether we think this would be justified or not, because depending upon the amount of information that is available on that antibiotic, if indeed this was given at a dose that would be considered of potential benefit to this child, then, you don't have to even ask the question whether it is a minor increase over minimal risk, because Category 405 simply says is it commensurate with the available alternatives and does not have any risk restriction.

So, if this is designed in a way where you have got the information, you have designed it, so that the dose is appropriate, you have got the PK data, et cetera, you finesse the issue of whether it is a minor increase over minimal risk effectively.

To me, this is similar to the MRI contrast in people who need the study, so I feel a lot better about this, but if this was the first time anybody ever got it, I probably wouldn't be as comfortable, so again, it

depends upon what data exists, but if there are sufficient data to where this could be considered a prospect of direct benefit, it is a very different context.

DR. FINK: But how can you consider it a prospect of direct benefit when PE tubes are being placed, because it has been well demonstrated that once you put the tubes in, antibiotic therapy is unnecessary, so there would be no potential benefit if you have gone ahead with PE tube placement.

DR. NELSON: Well, then, that is something I would have to take into consideration, but as a role, I am fairly liberal with the prospect of direct benefit. I agree that Phase I oncology studies have a prospect of direct benefit, so I think at least an IRB might put it under that category. I am assuming this child have been on antibiotics, may well still be on antibiotics afterwards, tubes doesn't stop all o otitis, so it is debatable at least.

DR. CHESNEY: Dianne, it says "investigational." Has it been approved in adults?

DR. MURPHY: Yes.

DR. CHESNEY: It has been approved in adults, but not yet approved in children.

DR. MURPHY: We recognize it is unusual for otitis media, but we were just trying to define a different approach versus the hospitalized child where you might have access, and you are going to be doing things to the child.

DR. FINK: In this particular case, I guess I would argue there is no increase over minimal risk, because the child is going to have the ear fluid drained and is likely to have or will have IV access established for anesthesia, so that the performance of the study other than the taking of the small blood sample from the indwelling catheter is not really increasing risk at all, and I would put this as a minimal risk.

DR. CHESNEY: Dr. Spielberg.

DR. SPIELBERG: This is based on the assumption that the antibiotic is indeed designed for that patient population, too, which also increases that child's potential long term benefit.

If it is a new antibiotic indicated for otitis, and the whole point of this is to figure out the

pharmacokinetics in middle ear effusion, that child is in a sense the perfect candidate for such a study, and since the tubes are going to be put in surgically anyway, that fluid is either going to be discarded or used, and use in this situation, it may well be a benefit to the child.

DR. CHESNEY: Dr. Edwards.

DR. EDWARDS: I just want to make it clear that I don't think that just putting tubes in is going to solve this child's total problems obviously, and I think that this child has probably been on a series of antibiotics, probably has resistant pneumococcus that will eat any antibiotics for breakfast, so that I think that probably there is a clear benefit for this child, so I think it really does not exceed a minimal risk.

DR. CHESNEY: Dr. Kauffman.

DR. KAUFFMAN: One additional point to consider, and that is if you agree that there is some potential benefit to the individual, I think that this also offers benefit to a lot of children in the future. In contrast to the MRI contrast, it is going to produce some useful information fairly quickly, and in probably the most innocuous way that that information can be gleaned.

So, it seems to me that you get the benefit versus risk assessment here is very different than the MRI example, and is very favorable for doing this study.

DR. CHESNEY: Susan.

MS. KORNETSKY: I just want to make a comment. In listening to the comments here, and what Skip said, I think, you know, we are using the minor increase over minimal risk as a threshold to say yes or no, but just because it may not reach that, the justification--there are two different issues here, and they are being mixed back and forth, and just, you know, even if something is not a minor increase over minimal risk, there still are other qualifications that need to be met, and we have really had no discussion about the other qualifications.

So, I just hear things being mixed here.

DR. WILFOND: I will respond to that. I think that both Skip and Susan's points are well taken. As one of the people who participated in writing these questions, I have been cringing because I really feel like I inadvertently have boxed people in a way that I really didn't mean to, and if I were to use this as a pretest for rewriting the questions, I would completely

change them.

I think really it is important that we ask the question about whether or not we think the study is justified, and not just focus on the question of minor increase over minimal risk, which is only one aspect, and I would like to turn the clock back and have a chance to redo that, but here we are.

DR. CHESNEY: Thank you for that confession.

Dr. Gorman.

DR. GORMAN: It strikes me as this discussion winds down that we may be laboring under another misconception. Most of the people around this table are obligated to follow NIH's rules because of their multiple project assurance numbers, and I would be interested from the representatives of the FDA how much of pediatric research is done in the institutions represented around this table versus out in the community where Subpart has no effect, and there will be a follow-up question, which is, is the FDA considering making Subpart D or some modification of that a requirement for studies done on pediatric patients no matter what the venue.

DR. MURPHY: I will take the second part first

by saying that really isn't the intent at this point, doesn't mean that that wouldn't be a potential approach. I can't give you an absolute number as to how many of the studies that are funded by industry, if you will, are done outside of institutions that would come under the federal regulations, however, it does occur, and that what we have seen is that particularly with the increased globalization of studies, that this is also at the stage of being performed in children outside of this country, too.

So, we really wished to make it clear that some of the studies--not the exact number, we can't give you--are going to occur in situations that will not be immediately under the regulations of HHS.

DR. CHESNEY: Dr. Nelson.

DR. NELSON: Just one follow-up comment on that. I wouldn't want to be misinterpreted in making an appeal for there to be a uniform standard that I necessarily assume that the standard, when applied, results in appropriate human subject protection.

What I might suggest, as a project, would be to look at studies that are FDA supervised, and whether

there is, in fact, a difference between what IRBs have done that are under MPAs and what IRBs have done that are not under MPAs to see whether or not Subpart D had any impact on (a) what the IRB did, (b) whether there was any difference in the consent forms or any difference in human subject protection.

So, there would be an excellent opportunity to actually look at whether Subpart D, which is sort of the language we are using, when out in the field, has an impact, and I am assuming that (a) you have the data, and (b) you have the regulatory authority to get the data.

Now, what you could do with the data after you have it is an open question in terms of publication dissemination, but I am assuming that that is an answerable question.

DR. CHESNEY: Dr. Walters.

DR. WALTERS: I have another system question, and that is, at several points this afternoon we have talked about the importance of getting access to the data that exists from studies in adults, from drug approvals, or INDs.

I wonder to what extent it's a problem to get

data like that, particularly data about similar products, but not identical products that might be made by another company.

DR. MURPHY: If there is a public health risk, in other words, let's say we have a class of drugs in which we have a problem that is arisen in one of the products in that class, and we are concerned about the other products in that class, obviously, we could go back and ask the makers of those products to look at what information they have.

I think the question of could we require sponsors to go back and provide information that they had not provided us, because the other question is, you know, how many studies have been on children and how much other information is out there that they don't submit, I think then you have a certain level of reason that you would have to have to go and require that of the sponsor.

Usually, FDA's standard is if there is a public health safety issue, and not being efficacious is also a safety issue, being exposed to drugs that aren't going to do what they are proposed to do, but we hopefully would not have approved them for that, so usually it is a

safety issue that would come up where we would have to go back and ask for that additional data.

DR. WALTERS: May I follow up for just a minute? With Phase II and III trials, there has been a lot of discussion of the importance of registries of clinical trials to avoid unnecessary duplication of effort, and I am wondering how far forward that kind of effort can be moved to try to avoid having children exposed to risks that they might not need to be exposed to because somewhere in the world, somebody has done a study on the same agent or a similar agent.

DR. MURPHY: Let me just attempt to answer registries. Fundamentally, the approach that we have laid out is that instead of doing two adequate and well controlled trials in children, that if you meet the standard that the disease and the response, the effect of the therapy, you can make those extrapolations are sufficiently similar between adults and children, you do not have to repeat the efficacy trials.

What you do need to do is provide the information how we can use this product if we have reasons for expecting that we don't have the proper dose

because of changes that are occurring or that we have safety data that we are going to need, or sometimes, as we are finding, is that we may need to look at a different endpoint that is being evaluated in children that was not evaluated in adults.

What I am trying to say is I don't think that we can say that developing a registry would approach the efficacy question. Registries are being developed to try to identify some of the safety issues in pediatrics.

DR. CHESNEY: Could I ask if we have a consensus on A, which is now a two-part question, No. 1, that the study does not exceed the threshold of minor increase over minimal risk, and secondly, that the study is justified in this patient population?

Are we agreed on that two-part question? All right.

Could we go to C. Could this study be done in children who cannot give assent? Comments? Are we in agreement that this study should be done in children who cannot give assent?

We were told it was an investigational antibiotic, so I think we are finished with Question 4.

DR. HUDAK: Could I just clarify one thing?

DR. CHESNEY: I am sorry.

DR. HUDAK: Going back to the MRI contrast agent, Questions A through D, I think just to make sure that I understand this correctly, patients who already have indwelling access or central lines, who might need an MRI for one reason or another, should also be eligible for participation, correct? For instance, the patient who comes in with trauma, who has a central line placed, and needs a diagnostic MRI, there is no reason why that patient would not be eligible to be enrolled in this study.

DR. CHESNEY: That is my understanding.

DR. HUDAK: Okay.

Case Study No. 5

DR. CHESNEY: What is the impact of compensation on parent/child permission/assent:

A. Would compensation unduly influence a child's assent? Should a child be aware or told of compensation prior to giving that assent?

Comments?

DR. MURPHY: I just want to say that we brought

this forth because there are recommendations that they should not be, and yet it was quite clear to us that they are being made aware, and we just want to hear this discussion.

DR. CHESNEY: Susan.

MS. KORNETSKY: You know, when you talk about compensation, I think of it in different ways. I think about it as a reimbursement for expenses, and then there is the inducement part.

I absolutely think that individuals, especially parents, I mean I know we talk about the children should be told what is going to be reimbursed. As far as the inducement part, I have strong feelings that there shouldn't be a large inducement.

I like to think of giving a child a token of appreciation for what they have done--this is going above and beyond what it costs a parent to bring their child--gift certificates, toys, books, those types of things, and if it is not an overly coercive amount, I don't personally have any reason, don't see any reason why that can't be told to individuals.

I think we get into problems when we get into

large amounts that people are starting to feel are coercive, and therefore, we are saying, well, maybe they shouldn't be told up-front, but I think if you keep the whole amount as a reasonable amount, I don't see any reason why it can't be up-front.

DR. CHESNEY: Yes.

DR. KODISH: I think we need to think of this in terms of our duty to be honest with our children, and a structure where this information is withheld from them until after the study is completed, and then disclose, I think has the potential to result in mistrust between child and parent, between child and investigator.

So, I would argue that if we are going to take assent seriously, then, compensation needs to be part of that assent. I think there is a sense here that money is a tainted part of this whole process, and maybe that is not necessarily supported.

DR. CHESNEY: Norm.

DR. FOST: I agree with both of the previous comments. I would just make a plea that the word "coercion" be removed from this discourse forever. Coercion means the use of the threat of force or

threatening people with deprivation of something that they are entitled to. None of that is going on here.

The ethical issue, if there is one, is exploitation of people who are poor, undue inducement, and so on, but coercion is just not what is going on, and I think it would be helpful to remove that word from the discussion.

DR. HUDAK: Why could not one inform the child about the level of reimbursement after the child makes a decision to assent, so that it doesn't influence the child's decision to participate or not? Would that be wrong?

DR. CHESNEY: Ben.

DR. WILFOND: I would say two things. One is to sort of extrapolate from Eric's initial point about the notion of the tie between assent and the compensation. I think John, during his talk, argued that one of the reasons for assent was--Ellen's talk rather--was the notion of respect for the individuals.

So, it strikes me that if your justification for assent is respect, and as part of that you are withholding information, that does present a very complex

message.

Secondly, certainly in the studies I have been involved with, with children, particularly the venipuncture studies, it is precisely that the possibility of $5 or $10 that the child weighs about whether or not they are willing to have themselves stuck, it seems that it is not unreasonable to present that to them, so they can make their decision.

DR. CHESNEY: Dr. Nelson.

DR. NELSON: What bothers me about the whole discussion of undue influence in compensation is the absolute lack of data, even in the adult world, about what influences decisionmaking on the part of the adults and what undue influence is, how do we operationalize it, how do we define it, how do we come to understand the level of compensation that makes people make decisions that we think they really ought not to make.

It is also unclear to me that we necessarily should treat children any differently than we would treat those adults if we had that data. Last week, I asked three, 11-year-old children (a) how much money it would take for them to want to be in an overnight PK study, and

the range was about $90 to about $200, and that was based, not on their assessment of risk, but on the time that they had and the fact that they had better things to do perhaps than spend their time in the hospital in a PK study.

When I told them that some people would argue that they shouldn't get as much money as an adult should, their reaction was that that was unfair, and when I said--I asked them why, and their reaction was that we are people, too.

So, I am not saying that that is--I don't intend that anecdote to be an answer, but I think there is a lot of bias in this discussion and absolutely no data to help us decide this even in the adult situation.

I think we can argue there is undue influence all over the place, and it would be nice if we can, over time, get some clarity on this.

DR. CHESNEY: Dr. Fink.

DR. FINK: I think one of the things that has not been looked at adequately is whether the study itself can be structured so that participation in the study is actually the compensation.

We did a three-day stool collection study in CF patients, where ahead of time the parent and the child involved knew they were going to be put up at a hotel in town, they would get free ordering from the menu, but there was no compensation beyond the fact that they got a nice three-day vacation at a nice hotel.

I think that that is one example of where you could actually structure the compensation as part of the study, and you would get away from this whole issue of undue influence because it would be right up-front, this is what the study involves, here is the negatives, here is the positives, and we are not talking money, we are talking the environment of the study and the fun you have during the study that you wouldn't have otherwise.

DR. WARD: Shouldn't the regulatory step be at the IRB approval level of the protocol rather than the level of reimbursement for their participation?

DR. CHESNEY: Do you mean shouldn't the IRB make this decision?

DR. WARD: Yes. That is, if the protocol is appropriate in who should be included and excluded, that the money should not be the rate-limiting step in this.

Rather, it should be whether this is a well-designed study that will derive benefit to the participant and their family, and if we have all done our jobs right and designed the protocol and approving the protocol, then, the money should not be the rate-limiting step about whether they participate or not.

DR. FOST: The protocol comes in with the investigator saying even though I think this is approvable under Subpart D, I can't get enough people to come in and sign up for it even though it meets minimal risk criteria, and so on, and so forth, so they are asking for an opportunity to induce people to come in with gifts or rewards.

Just one comment on gifts. There is one that you don't need data to discuss or even possibly resolve on ethical grounds, for adult studies, it is common now to pay thousands of dollars to get adults to come in, volunteers, for example, to stay for many, many nights in a clinical research unit, and so on.

It is just work, it is just blue-collar work, that's all. Almost nobody is going to do it out of altruism, and lots of people will do it if you pay them

enough. In general, at least our IRB doesn't have any problem with that. If healthy people want to go get stuck a lot, that is no different than wanting to work on a construction job or play football or anything else that is very risky.

But that argument will not suffice for a 3-year-old or a 6-year-old. That is, we don't think it is okay to offer a 3-year-old all the milk shakes he wants for the rest of--or all the ice cream he wants for the rest of the year to get him to do something, because he or she can't weigh adequately really the risks and even the discomforts perhaps of doing it.

So, there is no question that some kinds of studies call for inducements or at least require inducements to get a large enough sample size, and the question is--I will state it as a conclusion--I think what we would allow for consenting patients, we would not allow for children, because they can't make that judgment.

Secondly, we are a little worried about whether the money really will go to the benefit of the child also.

DR. NELSON: If I could just briefly respond. I think Norm did jump into B, which is appropriate, because I would be as worried that the compensation issue impacts on the parent's ability to judge the risk-benefit issues, and if the IRB thinks it is an acceptable risk-benefit issue, and if the parent thinks it is an acceptable risk-benefit issue, it is unclear to me why you shouldn't give that many milk shakes to a 3-year-old.

DR. FOST: Increases the risk.

DR. CHESNEY: Dr. Gorman.

DR. GORMAN: As long as we are in the world of anecdotes, our IRB recently approved a central study, and at the top of our consent form it said about 30 centers will be participating in this study, recruiting about 1,500 patients nationwide.

One human subject, after reading and approving to go into--you know, signing the consent form, called up the IRB and asked for the list of the 30 centers. When we inquired why he wanted that information, because he had already enrolled in one, he wanted to bid his services. He wanted to see if there was varying compensation between the different centers, and since

this was an inpatient study of some duration, it might make some sense for them.

They were doing their own cost-benefit analysis. I feel, having sat in the room when the discussion was about separating the assent from the compensation, that there still is an argument. I understand the concern about deception for children, but I think there is some concern that you have to get an approval that you are going to join the study and then decide on what the benefits are monetarily-wise past the token.

I don't find it a convincing argument that you have to tell everything to the patients, everything good that is going to happen to them, assuming the money is going to be good, when you are giving them what you are hoping to be informed consent, which is mostly risks, telling them what could go bad.

DR. CHESNEY: Yes.

DR. SZEFLER: The rules have changed, but in our IRB, we have to lay out all the compensation ahead of time, so it is right in the consent, and how it is prorated, and that is going to come from adults because the adults have done the same thing you said, and now we

have to kind of put that all out there.

So, when the patient or parent reads the consent, it is all there in terms of the compensation and how it is going to be prorated and how it is going to be done. They don't get it at the end. So, these are all things that are done as part of the IRB process.

DR. GORMAN: But in your IRB, does the patient, the pediatric patient read the consent or just the assent?

DR. SZEFLER: If they are capable of reading the consent, they read the consent, too, not just the assent.

DR. GORMAN: It is just the IRB leaves the compensation out of the assent part. It's in the consent part.

DR. SZEFLER: The assent is very simple. It is just a few paragraphs just to make sure they have been told it is our duty to tell them and the parent what the study is about, and as I understand it, the regulations are becoming more and more strict, that you have to sit down and go line by line. This is what I heard at our last meeting that you have to go line by line. It is not just a matter of letting them sit there and read it all.

Some of these are seven pages.

DR. CHESNEY: Norm.

DR. FOST: One point. If you were going to give the money or the reward, or whatever it was, after the child consented or assented, then, we are not talking inducements anymore. Inducements, by definition, have to be discussed ahead of time.

So, there is no need to have substantial or worrisome amounts in that case. You are just talking now about token amounts, gratuities, or ways of expressing your appreciation.

DR. SZEFLER: Our IRB is very much against anything that borders on the line of an inducement. They will look at those numbers, and actually in our situation, for procedures we do, and many of our procedures are fairly uniform, we have fixed costs that don't vary between protocols, and our IRB looks at those very closely and says you have exceeded it, you have to cut back.

DR. FINK: I think knowledge of what may be expected is also though one way of decreasing the risk. Just at a clinical level, we give out stickers and

lollipops anytime the child has blood drawn or a flu shot, and it makes them much more cooperative with the clinic visit to know ahead of time that if they put up with the flu shot or getting their blood drawn, they get the sticker and the lollipop, which I don't know if that is an inducement or a reward, but it helps them cope with the anxiety of the procedure, which is a positive thing.

I think in research studies, I am not sure why there shouldn't be something similar, that they should know about it up-front, and if it helps with them cope and assent to the procedures involved, I am not sure what is wrong with that.

DR. CHESNEY: Dr. Walters.

DR. WALTERS: I think for both consent and assent, the assumption is that the individual involved can say either yes or no, and with adults, I mean it seems as if we need to know what the whole deal is before we say yes or no, and I really think the burden of proof is on someone who says it ought to be different for assent.

If a child can say no, then, the child ought to

know what the whole deal is and then decide whether to say yes or no. You could only trick the child once. It wouldn't work after that. That is kind of a pragmatic justification for being truthful the first time.

DR. FOST: I just remembered the other point. One of the justifications that has been offered for enrolling children in non-therapeutic studies is to teach them altruism. You can't have it both ways. That is, either we are basing this on contract or we are basing it on altruism.

So, I think if there is going to be a rule on it, the rulemakers should decide which of these things they think is the correct model for recruiting children.

DR. CHESNEY: I haven't heard any--to me, the issue is whether a child, who is 8 years old, can weigh the gift or the inducement versus, you know, whether they are aware enough to weigh one versus the other.

You made a very good point about the 11-year-olds being very realistic, it's my time, and so on, and I have done a study with teenagers, and they very clearly were weighing it. I wonder, have any of you had the experience of working, doing a study in 8- or

9-year-olds, where you felt that if you had offered them more, they would have agreed to it than what you were offering? Yes.

DR. SZEFLER: The adults in particular have become very shrewd, especially if you are doing multiple studies in similar medications, and they weigh these packages very carefully, and they will turn down one over the other and kind of shop around.

I would hope they don't do as much with children, but children kind of pick up on these kind of habits, too, unfortunately, more so in the teenagers than the 8- to 9-year-olds, but I think the rewards are part of their--they come in many ways.

I think it is not just money, it's certificates and things that make them feel important, that they are an individual that is contributing to an important study. Sometimes the level of that significance is more important than the monetary in some of the children, but they do weigh those numbers, and it comes from the adults unfortunately, especially in a center where there is multiple studies available, they compare cost and kind of say, well, I got twice as much for doing that.

That is one reason why in our center, we try to balance those costs and base it on procedures and amount of time.

DR. CHESNEY: Well, on Question A, it seemed like we had agreement on the second part, that the child should be told up-front, that was an issue of respect and trust, and so on. Are we in agreement on that?

The first part, would compensation unduly influence a child's assent? Yes.

DR. KODISH: I think we need to be cautious about how we think about children making decisions, and avoid imagining a situation where an 8-year-old is making a decision in isolation. Eight-year-olds make decisions with the guidance of their parents, if they are making decisions at all, or it is a general flaw in how we think about ethics today, to think that people are individualized, atomized decisionmakers.

I just want to make sure that we don't lose sight of the dialogue and the joint decisionmaking that goes on I think in most families.

DR. NELSON: To follow up on that, my difficulty with the undue influence is really knowing what it means,

and I am not sure what it means in the adult world. You know, one hypothesis, given my appeal to have data, I won't suggest it as a conclusion, is it is as likely that the knowledge of a parent's prior permission for that child to be enrolled in that study could be as influential in an undue fashion against the child's own assessment of risk as any compensation that you might offer.

So, we need to just be cautious about the conclusions we draw in the absence of any data.

DR. CHESNEY: I think that is an excellent point, and if I understood correctly, you are making the same point that if a parent came across very positively, as Ellen does, for her children, and altruism, and so on, theoretically, it wouldn't matter if you offered them $200, because they risk going against their parents if they didn't agree.

So, that could be as or perhaps more important than the physical compensation, if you will.

So how do we answer that? Some form of compensation could unduly influence the child's decision whether it was parental support or what have you.

Dr. Gorman.

DR. GORMAN: I think the developmental stage of the child becomes important, as well. Adolescents, as they progress, seem to have less and less assessment of risk or less and less a realistic assessment of risk, and therefore, the monetary rewards may become a bigger inducement, because their assessment of their potential risk goes way down.

DR. CHESNEY: Thank you. Have we addressed that adequately, Dr. Murphy?

DR. MURPHY: Yes. We wanted a general discussion of these issues, and that is really what we are receiving. Thank you.

DR. CHESNEY: Part B. Does compensation compromise a parent's permission to allow participation of their child in a clinical trial? How would the nature, amount, and recipient of the compensation affect this decision?

Additional comments?

DR. NELSON: I think it is certainly a possibility and particularly if they are concerned about the parents pocketing the money that is intended for the

child. Again, in the absence of data, but based on our own bias, we had one study that went through our IRB, which was a tilt-table test for adolescents where we felt that the child would be in a better position to say no during the performance of the study, and that the fact of compensation in the presence of the parent, that of the two, the parent would be more likely to say keep with it, Johnny, keep with it, you are going to get money.

So, we actually excluded the parent from the room during the conduct of the study, feeling that they were actually a counterforce for protection. Again, no data. That was our bias on that particular study. So, I think it often could impact on that permission.

DR. CHESNEY: Dr. Luban.

DR. LUBAN: I would also like to point out that not all studies have compensation attached to them, and if we end up mandating rules that include compensation, we are going to cut out a large amount of good scientific data collection that is exclusive of reimbursement to kids or to families.

DR. CHESNEY: Thank you.

Dr. Clayton.

DR. CLAYTON: I would just make the point that history teaches us, that parents do not always act in the best interests of their children or even contrary to the interests of their children, so it really seems to me that this is far the greater issue than whether the money is an inducement, the money, if it actually goes to the child, is an inducement to the child.

I, like Dr. Fink, have had the experience where children feel better about stuff that they are averse to happening to them because they know they are going to get a sticker or get a certificate that says you are a good guy because you had your nose washed, or that they feel better about being brave because they are doing something--I mean I actually think that those sorts of things, with the kinds of amounts of money that we are talking about with kids usually, you know, are really far less problematic than the concern that a parent, who is not after all going to be the direct bearer of the risk, is going to let their child be subjected to something, that if they were the one, they wouldn't do.

I have to say that as between A and B, B is the big issue. I think A is really very minor by comparison.

DR. CHESNEY: Ben.

DR. WILFOND: I sort of agree with that, Ellen, but I am almost struck that the amount is more important than the recipient for the following reason. Even if you give the money to the child instead of the parent, if the amount was sufficiently large in terms of the parent's decision, that would still be money that they could forego in terms of otherwise spending on their child.

So, for example, even if you gave a very large gift certificate to K-Mart, that benefits the parent in the sense that now their child has gotten a gift that they otherwise didn't have to provide the money for, so I really think that the issue is more the amount than who it goes to, because they benefit potentially both people.

DR. CLAYTON: I guess I really was saying that because it seems to me that no one actually seriously considers giving large amounts of money to children. I realize that children think that is utterly unjust, that a big person gets more money than a little person does. No one has a greater sense of justice than a child, particularly when they are on the short end of the stick.

But I think really, you know, when we talk about

the amounts of money we give to children, they are almost always really pretty small, and the big issue with the larger sums of money is that whether we like it or not, they go to the parents. I mean that's it. The parents get it, and that is where the inducement and the potential for abuse lies.

DR. MURPHY: Would you clarify small amount of money?

DR. CLAYTON: Certainly the amounts of money that I have typically experienced being offered to children are in the neighborhood of $10 to $25. Admittedly, that is not so--

DR. MURPHY: Again, we are not going to come out and say you can only offer this much. I just wanted to give you some background that we are receiving proposals where it is not uncommon for the child to be offered a $100 certificate and the parent be offered a $100 or $200 certificate, so that those amounts of money are being offered.

DR. KODISH: And we do have evidence to suggest that there $300, $400 is not at all uncommon, directed to the child, but, of course, the parent is the one that

gets the money.

DR. CLAYTON: Really, the amount of money, I mean the parent is going to get it, and I think we have to recognize that parents are compromised decisionmakers. They are proxies, and we can't forget that.

DR. KODISH: So, you just mean it in the sense that they get the check, they cash it, put it in the bank, it goes on the withdrawal slip, that sort of thing.

DR. CLAYTON: They have access to it if they want it.

DR. CHESNEY: I was thinking, Susan's example of not giving something large in amount, but maybe a $10 gift certificate or a plastic airplane, for a good parent who can't provide that themselves, it seems to me they would urge the child to participate because they feel like that is a good thing, they are giving their child something that they wouldn't be able to provide them themselves.

So, to me, even that might unduly influence a parent, I don't know.

Dr. Gorman.

DR. GORMAN: I am having trouble, and I have

always had trouble with this child-parent divide. I acknowledge that I don't live in an ideal world, but the concept of family benefit is not exactly foreign to me, where a good thing that happens to one member of the family, if the mother wins the lottery, the child gets to live in the new house.

I don't think that the concept of this divide parent versus child is as dramatic as maybe we make it sometimes.

In response to the small question, it depends on what we ask the children to do. If you are going to do a year-long antidepressant study, and you are going to give a child $300 for 50 visits, and God knows how many EEGs, MRIs, and whatever, I would say that you are not appropriately valuing their time or risk.

If you are talking about an antibiotic study, a PK study for one day, and you are talking about $300, I again don't think that is terribly inappropriate, and I don't see why, and maybe this particular pediatrician really rankles at the fact that we get paid less for doing exactly the same stuff as big people doctors.

I don't think our patients should suffer under

the same injustice.

DR. CHESNEY: Dr. Kauffman.

DR. KAUFFMAN: I was just going to say that inducements come in many forms, and sometimes we are surprised. There is currently a study going on in infants, first year of life, at our place, and they thought that to avoid inducement, that each month when the child comes in, they would give the parent a month's supply of disposable diapers as a nice token thing. It would benefit the child and the family in general, and so forth.

It turns out parents kill for disposable diapers. It is an enormous inducement. How could we have known?

DR. CHESNEY: Any other comments? Do we have a consensus on this? Does compensation compromise a parent's permission to allow participation of their child in a clinical trial? Yes.

How would the nature, amount, and recipient of the compensation affect the decision? It seems to me if the recipient were the parent, that that would definitely affect the decision.

Dr. Nelson.

DR. NELSON: It sounds to me like there might be some general agreement among those with IRB experience, that you try and structure the cash in a way that the parent is compensated for their expenses.

Now, parental time I think is a difficult issue, but at least for expenses in that the parent shouldn't earn money out of putting their own child in a project, that somehow that compensation of time should go to the child.

How you actually get that to happen in a way that the parent can't then undo, if we don't want to be in the business of policing, I think is an open question, and whether gift certificates are any better than giving a check or giving--cash obviously would be easier, et cetera--those are separate questions, but certainly trying to structure it in a way that it is clear that the child should be reimbursed for participation or should be compensated for participation in a way that is different than just the parent's expense in bringing that child to the study, I think is the way that we generally try to approach it.

I have no data to know whether it works.

DR. CHESNEY: Dr. Edwards.

DR. EDWARDS: I think if one looks at the statistics in terms of the studies that are being done in medical centers and studies that are being done in other places, a decade ago they were almost all being done in academic centers, and now I think it is about half and half.

So, I guess one question that I have, as I listened to all this, is are we continuing to be ivory tower, are we looking at what it is in the real perfect world, and we are being so ivory tower that we are continuing to do the right thing, but in the meantime, increasing percentages of the studies are being done in scenarios, you know, maybe 75 percent, next 10 years, maybe 100 percent.

So, are we going to take these very important and very ethical and important discussions, are we just going to raise the bar in the academic centers, so that we are going to totally put ourselves out of business, so that all the studies are being done at other places that aren't jumping these bars.

DR. CHESNEY: A point well taken. I think several people have mentioned or raised the issue of whether these new recommendations should be across the board as opposed to just academic centers.

Yes, Dr. Clayton.

DR. CLAYTON: I wanted to respond to Dr. Nelson's point about compensating parents for their time, and say that I actually think that there is a strong argument that can be made that some compensation ought to be made.

I remember the comment being made earlier in the day that there are issues about whether you give the woman who is an investment banker more money than you give someone who works at Burger Doodle.

I must say that it is particularly the parent who works at Burger Doodle who I am most concerned about, because it is really clear that if mom is an investment banker or a general pediatrician or whatever, that she has somewhat more flexibility in arranging her life to get the kid into the study, whereas, if you work at Burger Doodle, first of all, taking time off is hazardous to your job and other things.

I would say that I would argue pretty strongly that at least--and I realize that this offers an element of inducement that we may be worried about--but the idea that people whose lives are already fairly stressed, that not only the child, but also the parent needs to be making sort of this altruistic gift to the greater good is a little bit unreasonable, it seems to me.

So, I would argue pretty strongly that at least some sort of compensation ought to be available for time, and I am particularly interested that it be tagged at the level of those who don't have a job like mine.

DR. CHESNEY: Dr. Walters.

DR. WALTERS: I just wanted to observe that analogous problems exist in other biomedical spheres. The bidding on human egg cells has been in the news during the past month or two in particular, but even before that, the American Society for Reproductive Medicine was debating what it is that a woman is compensated for in receiving whatever the number of thousands of dollars is for one cycle of hormonal stimulation and one group of harvested egg cells.

We have similar issues with the plasma

collection system and whether it is possible to have it be totally without payment.

I think more and more people are rethinking the issue of whether there should be any kind of recognition of families who donate organs through tax credits or some other mechanism.

So, this is not a unique problem to biomedical research involving children.

DR. CHESNEY: Thank you.

DR. SZEFLER: Just one point that I was going to add, because we keep kind of talking science, and the science is only relevant in discovery. As we cross the bridge of making this kind of testing, not only a science to get the new information for labeling, but it becomes a requirement, there comes a time when there is changes in formulation and just a required level of testing where it is not science anymore, it is part of the business package.

So, there is a difference in terms of what would be considered, and we avoid mention of science versus a requirement in terms of labeling, and I don't think we have separated those out enough, and kind of said where

did those bridges and that kind of separation get crossed, because I think the spirit of the Academy of Pediatrics and the drug labeling was to advance the science, and the inducement and the carrot is to the industry, and you can see that as a reflection of the types of products that are coming in.

They are the products that have the most to gain. I think where we have seen some lack of product coming to us, ones that are off patent, and those need information, but then there is going to come a time where it is going to become a requirement, and that no longer is science.

I don't think we can put the position of altruism. It's only altruism for a company who is going to make a profit, and there is no profit-sharing, and that is an issue, I think, that you brought up, where we are talking about genes and who has got ownership, and those kind of things.

I think the same issues are going to come up in this area, and I am not sure how to wrestle with that, because if the company is going to be required, they are going to have to do the studies, and if they recognize a

profit, they are going to be willing to offer more, and how do you stop that. If they decide I need 10 more children to complete this study in two months, they are going to be willing to give more money because their profit margin is there.

It is not so much whether we do it, it is how are we going to stop it from happening, and I think, Ralph, when you showed your advertisement there, those are the ones we cringe to think about, where ads come, you know, we need children. I think those are where the science gets soiled, and I think those are the kind of things that you are asking questions about, and I don't think we have addressed that for you, where do we draw those lines, because I think there are costs that we can sit back and say we are comfortable with in terms of reimbursement, but then there are a layer of costs that then start to become inducement, and I am not sure, how we put that into legislation or guidance.

I think that is what you are asking in these questions, at least that is what I sense.

DR. CHESNEY: That is a very good point. That is going to be a real challenge for IRBs five years from

now when every drug has to be tested, and there aren't enough children to go around, and we want the information, but the only way to get it is to pay more.

DR. SZEFLER: I think one category of drugs that we are facing--and Steve mentioned it before--is antihypertensives. There are so many drugs that are a big profit in terms of hypertension management, but hypertension is more of a prevalent problem in adults, but yet the exclusivity provides a margin of profit in drugs that may not be extensively used in children, so those issues are going to become more prevalent.

That is why I was interested in the ophthalmology question, and I think you answered it by saying that this is a relevant drug in a pediatric population or otherwise it could be used to do pediatric studies in a population where it is not relevant, but yet it provides guidelines for use in a small population, but you answered that by saying it would be used in the population.

So, I think we have to be very careful about how much of a requirement is made and that inducement.

DR. CHESNEY: Excellent point.

Dr. Danford.

DR. DANFORD: It does raise one other question, and that is will we be dealing with a particularly at-risk population, the offspring of employees of pharmaceutical companies, as these issues come up, will their parents be offered inappropriate inducements or carrots and sticks that we would rather not have them offered, and how can we address that.

DR. CHESNEY: Your benefits depend on how many of your own children you enroll.

Dr. Fink.

DR. FINK: I think the question should be broadened because I am worried that compensation will affect parents' consent for their children, but I think we also maybe should broaden the question to say will overcompensation of researchers potentially influence which studies they choose to participate in and push, because I think there is an equal risk that institutions and researchers may jump on those studies that are not the best science, but that reimburse the largest amount, and therefore, not necessarily the best science or the most needed studies will be performed, but the best

funded studies will be performed first.

DR. CHESNEY: Dianne, you are going to have to have a lot more meetings to sort some of these out.

DR. SZEFLER: Just one additional comment I might make, we seem to kind of be talking about the drug and then the study design, and then the risk-benefit analysis, and perhaps maybe the regulatory authorities might be thinking that maybe in children, it needs the reverse process, that whoever is proposing the study justifies a need in the pediatric population, and then builds the opposite way to say this is an area of need, this is why, these are the statistics, whether it is taste or cost, and then kind of builds to the justification of the protocol design.

I have read hundreds of protocols, and they generally start out by talking about the drug and why you want to study the drug, and then build into the protocol, and then there is a paragraph at the bottom, almost towards the end, that talk about risk-benefit analysis, and maybe we need to be thinking of the reverse in the invitations to do the studies.

The way the IRB looks at it, it would certainly

would ease our job if those kind of things were laid out to us rather than we have to think about it, make the decisions, and then make the separation.

DR. CHESNEY: Dr. Walters.

DR. WALTERS: What the last few comments have suggested is the broader context, and I think it is not limited to the commercial sphere. I have sat on data monitoring committees for multi-center trials, and each center participating has contracted to recruit a certain number of patients to participate in the trial, and we always are quick to identify the laggards, those who are falling below their recruitment goals.

We crack the whip and say if you don't meet your recruitment goals, then, clearly, the funding agency is going to have to adjust what you are receiving for your participation in the trial.

So, there can be a variety of influences on researchers that can be passed on into their consent transaction or assent transactions with candidates for participation in the trials.

DR. NELSON: It strikes me that there could be some room here for perhaps a guidance document. For all

I know, there may well be one, but since I don't know all of the guidance documents that exist on appropriate recruitment techniques, for example, on our IRB we would not allow an investigator to recruit from family members or colleagues or children of family members that are within their division or section.

The argument there is that that is not voluntary, it might be informed, but it is not voluntary consent. Although that would not have the force of regulations, it might be an arena for a guidance document that would sort of stipulate some of these ground rules. I don't know if something like that currently exists or not.

DR. CHESNEY: Susan.

MS. KORNETSKY: I think I started this morning by talking about the need for guidance documents for IRBs. What I see will probably happen after this discussion, I think a lot of these issues are going to fall to IRBs to deal with, and I think the better educated they are, and the guidance that they are given, I think the better off we will all be.

DR. CHESNEY: Thank you.

Dr. Gorman.

DR. GORMAN: I think we have had a somewhat useful exercise trying to build some case law into general guidelines, and knowing how my own IRB has developed over the years--I don't own this IRB, this is the IRB I sit on--we have generalized, and hopefully, maybe this will be the algorithm we use as we go into placebo-controlled trials the next time where we will start to develop some case law where we hopefully can generalize under guidelines, which I guess was the object of today.

DR. CHESNEY: Dr. Murphy, do you have any other questions of this--present company excluded--erudite group?

DR. MURPHY: No. I did want to--I am exhausted--I did want to thank the participants sincerely. I know that many of you have been wondering why you were here today, now, what are we going to do with this information.

Before I do that, I did want to take the opportunity to thank Dr. Wilfond, Dr. Hirschfeld, Dr. Roberts, Drs. Temple and Behrman, who have participated

in collecting opinions and expertise to put this meeting together.

We are learning about our cases, but I also have to tell you that in trying to protect the innocent and redacting these cases, sometimes we may have over-eliminated information, but we do appreciate your struggling with some of the generalities because we did want to use, as we said, actual situations.

This has been a very, very helpful discussion, and what are we going to do with it. One of the things I have tried to make clear is that we really are not anticipating rulemaking. That was not why we had this meeting.

We were anticipating that we wanted--first of all, I think clearly stated there are so many things that impact a decision, and ethical decision, that it would be I think hubris for the FDA to say we are now going to be the regulators of ethics. That really was not the intent here.

What we wish to do is to continue to use the systems that are in place. What we will do is we will review the discussions that we have had. We normally

film our Advisory Committees, but we particularly are planning to use this film for internal education and to develop this whole process as to how to approach these issues, both within the FDA, because much of this is new for many of our reviewers also.

We want to develop and enhance the educational activities, if you will, with our IRBs. We have had a communication almost two years in the process to try to develop some comments to the IRBs, at a minimum to make them aware of the tremendous activities that are going on in this field and some of the issues that we have seen addressed today, with OPRR, establishing and continuing our communications with them, and with our sponsors, with the industry that we regulate as to ongoing conversations with where we are in this process.

This committee will continue to play a pivotal role in that we will be coming back to you, as I said, to discuss placebo-controlled trials. We will be taking the information that you have discussed today and hoping that we can get all of the committee back, that we don't have to go through the education process, because we really felt that part of what we were doing today was educating

us and the committee into how you would approach some of these issues, and we will use this discussion to go forward with the discussion on placebo-controlled trials.

Will we develop a guidance for IRBs? Guidance, as you heard, doesn't have regulatory enforcement power, but it does have tremendous effect, and I think at this point, we are really not ready to do that.

We are simply trying to get forth to, if you will, reviewers, to industry, the issues that we see coming forth because of the tremendous activity in this field. After we have explored many of these topics, will we be able to incorporate some of this into some of our guidances? We would hope so, but whether we will design a separate guidance, I would say at this point the answer would be no.

Can we incorporate aspects of these issues? Certainly I know that the ICH document that we are working on with Steve does address some of these issues, and we are also developing a pediatric clinical trials guidance that we may wish to incorporate some of these discussions and comments.

I thank you very much for your discussion here

and look forward to seeing many of you on the same wavelength, if you will, ethical discussions of pediatric trials.

Thank you.

DR. CHESNEY: I also thank you all very, very much for your comments. The greatest fear of sitting here is worrying that people won't say anything, and you certainly did. That was not a worry.

Thank you.

[Whereupon, at 5:20 p.m., the proceedings were recessed, to resume at 8:00 a.m., Tuesday, November 16, 1999.]