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CENTER FOR DRUG EVALUATION AND RESEARCH

PEDIATRIC ETHICS SUBCOMITTEE OF THE
PEDIATRIC ADVISORY COMMITTEE

Wednesday,
May 11, 2011

8:00 a.m. to 3:05 p.m.

Bethesda North Marriott Hotel
5701 Marinelli Road
Bethesda, Maryland 20852

ALDERSON COURT REPORTING

MEMBERS PRESENT:

JEFFREY BOTKIN, M.D., Chairman,

SRINIVASAN DASARATHY, M.D.,

NORMAN FOST, M.D.,

LEONARD GLANTZ, M.D.,

STEVE JOFFE, M.D.,

LORETTA KOPELMAN, Ph.D,

J. STEVEN LEEDER, M.D.,

THERESA O'LONERGAN, Ph.D,

ALEXANDER RAKOWSJY, M.D.,

GEOFFREY ROSENTHAL, M.D., Ph.D,

LAINIE ROSS, M.D.,

KENNETH TOWBIN, M.D.,

ATHENA ZUPPA, M.D.

ALSO PRESENT ON BEHALF OF FDA:

WALTER ELLENBERG, Ph.D, Executive Secretary, DFO,

ROBERT "SKIP" NELSON, M.D., Ph.D,

MICHELLE ROTH-CLINE, M.D., Ph.D

A-G-E-N-D-A

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P R O C E E D I N G S

[8:00 AM]

CHAIRMAN BOTKIN: Well, good morning everybody. I'm Jeff Botkin and it's my privilege to chair this meeting at Skip's invitation and it's a wonderful opportunity to get together with friends and colleagues for a number of years, to talk about what is a particularly interesting and exciting domain. So, this will undoubtedly be a fascinating and productive session this morning. So, welcome to all of you who have come to participate in this discussion today.

One quick mechanical issue here. My understanding is that it's very helpful to use the microphones but we can only keep two microphones open at a time and so as the discussion begins, if you could catch my attention or Dr. Ellenberg's attention here, we'll get you on a list to move that conversation forward so that will work better than simply turning on your mic to gain our

attention.

So, our first order of business today will be to go around the table here and do introductions. So, Dr. Ellenberg, we'll start with you.

DR. ELLENBERG: I'm Walt Ellenberg, Designated Federal Official, Office of Pediatric Therapeutics at FDA.

DR. ROSENTHAL: My name is Jeff Rosenthal, I'm a member of the Pediatric Advisory Committee and I'm a pediatric cardiologist.

DR. FOST: Norm Fost, University of Wisconsin, pediatrician and director of the bioethics program.

DR. DASARATHY: Dasarathy, I'm from the Cleveland Clinic, I am a transplant hepatologist.

DR. JOFFE: Steve Joffe. I'm a pediatric hematologist and oncologist from Dana Farber Cancer Institute in Boston Children's Hospital and a pediatric bioethicist.

DR. ROSS: Lainie Ross from the University of Chicago, associate director of the MacLean Center for Clinical Medical Ethics, pediatrician and philosopher.

DR. GLANTZ: I'm Leonard Glantz. I'm at the Boston University School of public health. I'm a lawyer.

DR. ZUPPA: Good morning. I'm Athena Zuppa. I'm from Children's Hospital of Philadelphia. I'm a pediatric intensivist and clinical pharmacologist.

DR. ROTH-CLINE: Michelle Roth-Cline, pediatric ethicist, Office of Pediatric Therapeutics, FDA.

DR. NELSON: And Skip Nelson. I'm a senior pediatric ethicist in the Office of Pediatric Therapeutics, FDA.

DR. LEEDER: My name is Steve Leeder. I'm a division chief for clinical pharmacology and medical toxicology at Children's Mercy Hospitals and Clinics in Kansas City and my background is pharmacy and pharmacology.

DR. TOWBIN: I'm Kenneth Towbin. I'm a child mentalist and psychiatrist at the National Institute of Mental Health Intramural Program and also a member of the Pediatric Advisory Committee.

DR. ROSENTHAL: Good morning. My name is Alex Rakowsky, member of the Pediatric Advisory Committee. I'm the IRB Chair of Nationwide Children's Hospital in Columbus, Ohio.

DR. O'LONERGAN: Hi, I'm Terri O'Lonergan. I'm a bioethicist and director of research, education training, advocacy and the Child and Maternal Health Program in Colorado.

DR. KOPLEMAN: I'm Loretta Kopleman. I'm Professor Emeritus from Brody School of Medicine at East Carolina University and faculty affiliate at the Kennedy Institute of Ethics, and my specialty is philosophy and ethics.

CHAIRMAN BOTKIN: And I'm Jeff Botkin, pediatrics and bioethics at the University of

Utah.

Dr. Ellenberg?

DR. ELLENBERG: Thank you. I'm getting ready to make the opening statement for today's meeting.

Good morning to the members of the Pediatric Ethics Subcommittee, invited speakers, members of the public, and FDA staff. Welcome to the meeting.

The following announcement addresses the issue of conflicts of interest with regard to today's discussion. Today's meeting is considered in particular matters of general applicability and will discuss and make recommendations on a hypothetical protocol involving administering sub-therapeutic doses of drugs or biologics to a healthy population of children. There will be no discussion of safety or efficacy on the specific--on any of the drugs and no company is under discussion at the meeting.

This meeting will gather expertise to

provide advice to the FDA on the ethical considerations involved in doing these studies, including the following topics: assessment of risk of administering sub-therapeutic doses of drug or biological products, the appropriate subject population to utilize for these studies on children, and the referral process for such protocols for review by a federal panel under 21 CFR 50.54, losartan, omeprazole, midazolam, and caffeine, are hypothetical examples of chemical entities which are manufactured by many firms and are not in issue or part of the discussion before the committee.

The data and information that we will be provided and discuss during today's meeting is in the public domain. Based on the submitted agenda for the meeting and all financial interests reported by the committee participants, it has been determined that those individuals participating in the meeting do not have a financial interest that represents a potential for conflict of interest. In

general, the committee participants are well aware of the need to exclude themselves from involvement in the discussion of topics if their interests would be affected and their exclusion will be noted for the record.

We note that Drs. Leeder, Dasarathy, Fost, Glantz, Kopleman, O'Lonegan, Ross, Zuppa, and Joffe, are participating as temporary members. We have one open comment period today and it is scheduled to begin at 11:00 o'clock a.m. If you are planning to make a public statement during this period, please register your name at the registration table, which is outside of this room.

I will be available during the morning break to coordinate this activity. I would like to remind everybody to turn your microphones on when you're speaking and then turn them off when you've finished your statements. I would also like to remind everybody at this time, committee members as well as those in the audience, to turn off or

silence your cell phones.

And on a final note, the Office of Pediatric Therapeutics at FDA has recently inherited all the duties associated with coordinating both the Pediatric Ethics Subcommittee and the Pediatric Advisory Committee. We appreciate your patience and understanding as we work through and establish the procedures for the multitude of tasks that we have to undertake in order for these meetings to go off in a successful manner. However, we do welcome any comments that the committee would have and we'll take those into consideration to help the process for future meetings.

Just as one final reminder, today's meeting is considered of particular matters of general applicability and there will be no discussion of safety or efficacy on specific drugs and no company is under discussion. Thank you.

CHAIRMAN BOTKIN: Thank you. Skip is

going to give us an overview of our agenda and marching orders today. Skip?

DR. NELSON: Thanks, Jeff, and first of all let me welcome everyone to what I hope is going to be an interesting discussion that will, I think, move us forward in a particular area that's not been well-examined from an ethical standpoint as far as exploratory IND studies in pediatrics, or what some might call Phase 0 trials.

Let me just briefly mention the agenda. I mean, Steve Leeder has kindly agreed to give a scientific presentation to lay on the table some of the issues in conducting some of these studies, particularly in the area of clinical pharmacology. Then I'm going to give an overview of some of the ethical issues, and then Michelle will present to you the questions that we're asking you to tackle. And at that point the rest of the day will be tackling those questions.

Let me just, before Steve gets

started, address one question that may have come up in your minds. As this meeting was originally being conceived, there was a protocol that had been referred under 21 CFR 50.54, in other words, reviewed by a federal panel because the referring IRB had found that administering the cocktail for doing this study was a minor increase over minimal risk and they wanted to include healthy, normal children as controls and they felt that was not in compliance with subpart D 50.53--and we'll get into these things, I'm sure--and therefore they referred it for review. Upon that referral, we initiated that.

At that time, in anticipation of what eventually happened, we had a discussion about the importance of the topic independent of the review of the protocol and felt that the topic had not been adequately discussed and it would be useful both for the development of FDA guidance as well as for information to investigators to talk about the topic in

anticipation of the fact that eventually happened that the investigator removed the healthy control group from the trial and therefore the referral was made moot, if I'm using that term legally correctly. Leonard will correct me if I'm not.

So, basically, there is no protocol, but all of the information--there's plenty of publications--basically the protocol is in the public domain. We distributed to you Gil Burckart's consultation, which was about the protocol, and none of that was confidential. We just blocked out the institution, so effectively we can talk about the issues in such protocols with a concrete example before us, but I just wanted to make it clear that there is no recommendations on the table as far as whether something like this should or shouldn't go forward under 50.54 other than simply the implications of your discussion of the other questions.

So, I just wanted to lay that out

since that could well be the elephant in the room, and I just wanted to name it and dismiss it at the beginning.

So, I could take questions on that or we could just move to Steve's presentation.

CHAIRMAN BOTKIN: Questions for Skip? All right, thanks, Skip. And I would say, again, this is going to be a fascinating discussion today. Science and--clinical science moves forward, but for the most part the regulations have remained relatively static over the years, so this is generally an opportunity to see how these new, innovative ways to explore physiology and pharmacokinetics, et cetera, fit within the existing regulatory structure. As part of our discussion we may have an opportunity to see how, perhaps, the regulations or guidance might be changed, but for the most part our discussion is to see how these new approaches may fit within the established regulatory framework.

Let's move on, then, to Dr. Leeder's presentation.

DR. LEEDER: Thank you for the opportunity to come and participate in this forum. This is an issue that is of interest to us, our group, the Clinical Pharmacology Group in Kansas City, and we have been conducting phenotyping studies, what we call phenotyping studies in children, I guess for close to 15 years now, and most of what I'm going to be describing to you is some of our experience. These are with single entities rather than a cocktail, although a couple of studies have been conducted with two compounds in combination.

Just to begin with, I'd like to disclose support from the National Institutes of Health, and particularly NICHD. The grant support for the R03 and the R01 at the bottom both involve phenotyping studies in children and the R03 study is the earliest one and it is the one that I will talk about almost

exclusively.

This phenotyping study uses dextromethorphan, the over-the-counter cough suppressant as one of these phenotyping probes and, as such, is an off label use of the compound.

So, before we get to the goals of the presentation, I just wanted to go over a little bit of background that leads us up to why we want to do these types of studies in children. One of the things that we are concerned about most in pediatric clinical pharmacology is trying to understand variability in the disposition and response to medications that are used in children often when there is very little information to guide the use of those compounds. We know from adults that genetic variation is a large component of this variability and we know that environmental factors can influence drug disposition and response, but the issue that we have to deal with in children that adults don't have to deal

with to quite the same extent, is this change that's associated with development.

So, if you could just--you know, just think of the first 18 years of life--this is what we're really talking about here--and if you were to look at any five-year window--birth to five years of age, or eight to thirteen years of age, particularly if you have children in that age range--you know that there is a considerable amount of change that takes place over that five-year period of time.

If we switch to the ages of most of us in the room, let's say 40 to 45, 50 to 55, sure, there's some senescence going on, so there is a little bit of physiological change, but it's nowhere as dramatic as what takes place in the pediatric years and it is that sort of variability, the developmental sorts of variability, is the thing that's going to cause us the most problem as we try to understand how children are going to respond to medications.

And so the concept here is that when

we look at genetic sources of variation, our genotype--our genetic makeup is not going to change as we grow and develop. There might be some modifications to that DNA sequence, but the point is that for the most part the genetic code does not change. However, the phenotype, the physical representation of the data encoded in that code does change as we go from birth to 18 years of age when magically we become adults and beyond.

So, in the context of the effective-- safe and effective use of medications in children, what we are really concerned about is establishing the dose-exposure response relationship. You would not want to conclude that a particular medication is not effective in children simply because you didn't know the dose-exposure relationship or dose-exposure response relationship. So, this is really important to know if you are going to initiate clinical studies of a particular entity in children for the reason I just stated, that is

you do not want to conclude that it's not effective simply because you didn't understand this relationship and the dose was not sufficient to elicit a clinical response.

It's important to note that this dose-exposure relationship is a function of multiple processes and I'm going to be talking almost exclusively about metabolism or, more correctly, biotransformation in this particular presentation. And so in the context of developmental changes in drug biotransformation, it turns out that things are not quite as simple as we would like to believe. There are many different cytochromes, P-450, glucuronyl transferase, sulfotransphrases, and other gene products involved in drug biotransformation that have different developmental profiles, and I'll get into this in just a moment. We also know that transporters can also play an important role in drug disposition and we know far less about how these change as we go and develop.

So, from the perspective of drug metabolizing enzymes, there is an excellent review by Ron Hines from the Medical College of Wisconsin that has looked at the sum total of largely in vitro data that have been published to date on ontogeny, and he has broken up these different pathways into three different groups. The first group consists of those drug-metabolizing enzymes that are expressed at very high levels in the fetus--fetal liver, and not so much post-natal liver, and an example of that is cytochrome P453A7.

The trajectory of CYP3A7 is expressed at very, very high levels in the fetus. It's not there as a drug metabolizing enzyme. It is there to add the third hydroxyl group to DHEA sulfate to make 16-alpha DHEA sulfate, which is a precursor for estriol biosynthesis by the placental syncytiotrophoblast. So, this is an important step in the formation of estriol, the pregnancy estrogen of humans and high order mammals, so it's largely a developmental

function.

Group two are those pathways that are expressed in roughly equivalent amounts in fetal liver and in post-natal liver, but the group that we're most concerned about today are the group three pathways, these are ones that are not expressed in appreciable extent in fetal liver, but their expression turns on after birth. The trick here is that they don't all turn on at the same time. As we will see, cytochrome P4502D6 is an example of a pathway that turns on pretty quickly after birth. I will not show you any data, but of that list the last one CYP1A2 and some of the other pathways like flavin monooxygenases have even more pronounced delays in their ontogeny.

So, not only do we have variation that can be contributed by genetic differences or environmental differences, but particularly in the first three months there's a lot of variability as contributed by the fact that within a population of children, a given

pathway doesn't necessarily turn on at the same time.

So, this is a cartoon that sort of illustrates this concept of developmental trajectories. And so this is a hypothetical polymorphically expressed--anything that you want--let's call it a P450, and so here at-- shortly after birth, we can see each of these lines starts at a different place and in the first few years of life there is this increased developmental increase in activity, it peaks at some point and then may or may not decline to adult values.

There's also a subset of individuals who start low and stay low, and so these, for example, would be those individuals who are genetically deficient in a particular pathway. The point here is that if we were to phenotype or if we were to sample the population at the points in time, we might get completely different phenotype/genotype relationships, and it is this change in phenotype on the

background of a set genotype that is one source of variability that we are trying to tease out in children with these phenotyping studies.

So, the goals of the remainder of the presentation are just to review some of the science underlying these drug biotransformation phenotyping studies. We're going to look at how this information might be applied in a pediatric setting that might be different from an adult setting. I'm going to describe to you a typical phenotyping study that we have done at our institution. This particular study uses the cough suppressant, dextromethorphan, to look at the ontogeny or the developmental trajectory of cytochrome P452D6, and then how we can apply the results of that study. And then we will take a look at some of the other pathways that are targeted by the compounds that were in the hypothetical phenotyping cocktail.

So, let's attack the first component of the presentation.

So, a phenotyping study is defined as measuring the activity of a specific enzyme or transporter in vivo. There are also such things as in vitro reaction phenotyping studies that are usually conducted in a preclinical phase to try to map out what pathways are involved in the biotransformation or disposition of a particular compound, but for the purposes of today, we are going to talk about in vivo studies.

An in vivo phenotyping study generally involves administration of a preferably specific, but in most cases selective, and the reason I'm making this distinction here is that ideally you would like a compound that is going to be the marker for a single pathway so that you can infer what is going on with that pathway independent of an other modulating influences. In all reality, our drug biotransformation systems that we have evolved are highly redundant and so that means that multiple pathways can kick in and contribute to

the metabolic conversion of the compound and facilitate it's elimination from the body, so we really don't have any specific substrates although within accepting some tolerance, there are some substrates that are relatively specific.

The second phase of the study, then, involves a particular endpoint that gives you some insight into the activity of that pathway in a given individual patient or subject. The best measure would be a measure of either clearance or the inverse of clearance is an area under the curve or as a measure of systemic exposure, the product of concentration over time in the body. Sometimes what people will do is that you'll have a compound that might be metabolized to two or three or more particular metabolites and you may be most interested in the formation of one specific metabolite to give you some idea, some insight into the specific pathway. And in the dextromethorphan study I'm going to show you,

this is what, in essence we do, although it's not a clearance, it's a urinary metabolite ratio, but we are interested in one of the three major metabolites of dextromethorphan.

There are some studies that will look at a single concentration at a fixed or fixed time or range of times after administration of the dose, and then probably, the easiest to conduct, but perhaps the least informative, are those that involve collection of urine or saliva samples and look at the ratios of the drug and the metabolite of interest.

The general consideration here is that the change in the metric, whether it's clearance at one end or the metabolite ratio at the other end, reflects the change in activity of the pathway of interest and one can experimentally modulate the level of expression in a given individual, either by pretreatment with compounds that either induce or up-regulate the level of activity or inhibit or reduce that activity.

These types of studies are primarily done on adults.

So, one of the most important things that goes into the design of phenotyping study is the choice of the probe. Preferably you would like a compound for which there is already a considerable amount of information regarding the safety of that particular compound. Over-the-counter compounds are good, but certainly you would like to have something that has received regulatory approval for use in humans, in adults, and even better, in children. Generally speaking these will be accompanied by a considerable amount of safety data and generally there is also a fair bit of preclinical data on the metabolism or the metabolic pathways associated with the compound.

I say generally, because there are a lot of older compounds that are now being considered under the Better Pharmaceuticals for Children Act and we are finding that these

compounds are so old, they really don't have a lot of preclinical, in vitro, drug biotransfer information and data to guide us on how we might design a study or choose an appropriate dose for a pediatric population. And towards the end of the presentation I will show a slide that gives you an idea of how we work through some of these issues.

You want something that's going to be quantitatively important in the disposition of the compound. What I mean by this is that there are websites on the web where you can type in the name of a drug and find out what P450s, for example, can metabolize that drug, and there is a difference between a pathway that is capable of converting a drug to a metabolite, and one that is actually quantitatively important for the disposition of that compound in vivo, and that's an important distinction because what you would really like to choose is a probe that is going to be, let's say, 80 percent metabolize down the pathway

that you are interrogating in your phenotyping study.

Particularly when we talk about pediatric applications you'd want to minimize the invasiveness of the protocol, you really would like to have something that is orally administered as opposed to something that requires placement of an intravenous line, but you need to recognize that if the same medication, for example, midazolam is available by the oral and the intravenous route, that you're going to be measuring different phenotypes. Finally you want something that's going to be reproducible and you want to make sure that there aren't other factors that might obscure the endpoint that you're interested in.

So, I made this point before, genotype does not change but phenotype does, and this is particularly true for those processes involved in absorption, distribution, metabolism, and excretion. I'm not going to go into these in a lot of detail, but for example, in newborns,

gastric pH is actually more alkaline, less acidic, and that has implications for the absorption of some compounds. Body composition is actually quite important. The percentage of total body mass that is water, changes as we mature and we are now finding that things like changes in the ratio of liver mass to total body mass changes throughout childhood. It seems to peak in the two to five year range and this has been associated with the inability to see some genotype/phenotype correlations that are apparent in adults. We don't see them in children. And this is proposed as one reason why this may not be the case for specific pathways.

I'm going to talk in a little bit more about the drug biotransformation pathways and also renal function changes as children grow and develop, particularly in the in the first year of life.

So, I alluded to this issue of ratio of liver mass to total body mass being a little

bit of an issue, and this turns out to be important for the contribution of genetic variation in cytochrome P450 2C9 to a pharmacogenetic matter of considerable interest right now and that is warfarin pharmacogenetics in adults. In adult studies the genetic variation in this biotransformation pathway, CYP2C9 and in the target of warfarin, Vitamin K oxidoreductase complex 1, or VKORC1, genetic variation in these two genes accounts for roughly 40 percent, it varies depending on the study, a variation in the initial dose of warfarin in adults.

There has been one study conducted in children and it's a joint Canadian and European study, and in their study they actually found that genetic variation in those two genes accounted for less than 5 percent of the overall variability in initial dose, but age contributed 28.7 percent. So, completely different, and this is one of the issues that highlights why it is so important to study

these associations in children rather than just taking the adult experience and assuming, because of the lack of evidence, that the issues are going to be the same.

So, why do we do these types of studies in children? The reason why we started doing these studies was this issue of ontogeny, the question we were asking ourselves was, at what point will phenotype become concordant with genotype so that we might be able to start to use data, pharmacogenetic data, derived from adults. The issue here is that one cannot expect to see a phenotype/genotype relationship if the gene product is not fully expressed. If you extend that a little bit further, if the target of drug response is not expressed, it is possible, or almost likely, that you're not going to see the intended therapeutic benefit of a medication, and so while it's easier for us to measure drug metabolism, it is a little bit--well, it's a lot more difficult in many cases, to measure drug response, but really

what we would like to be able to know is when is the target of drug action fully expressed during development.

Another question that is important to us is the effect of disease state on the disposition of a particular compound. If you ask pediatric subspecialists what's different about their disease of interest that might be nominally similar to an adult disease of interest, you will often find that there are many, many differences. One of the areas that we are working a lot in right now is juvenile idiopathic arthritis and the pediatric rheumatologist in my group will tell you that is a very different disease than adult rheumatoid arthritis, and so there is no reason to expect that what works for adults will necessarily work for children.

In fact, there are also many diseases in children that do not have an adult correlate, so there will be no adult experience from which to inform our trial designs. And

then there is the issue of drug-drug interactions. If you have these developmental changes in a drug biotransformation pathway so that the drug metabolism pathway phenotype is different in different ages, will drug-drug interaction data in adults be equally applicable at--for children of different ages and developmental stages.

So, we got into this business and I joined Children's Mercy Hospital in Kansas City in 1996 having left the Hospital for Sick Children in Toronto at that time and we were very much interested in this whole issue of ontogeny, but what really stimulated the course of events for us was shortly after arriving at Children's Mercy Hospital, an orthopedic surgeon just walked into our area, on Friday--I remember it distinctly, it was a Friday afternoon, and he sat down and he had just had a little bit of a rough interaction with the mother of a three-month old where he had done a clubfoot repair, and while in the hospital the

infant had been controlled with pain--for pain, with morphine, but he had transitioned the child to codeine upon leaving the institution, and the mother was complaining about how the codeine didn't seem to be controlling the pain.

And so, we said, well--I think we may have said, duh, but that's not really important--cytochrome P450 is important for converting codeine to the active analgesic morphine and so it may be that--and this was a fact that he was unaware of at that time, this would probably be early 1997--it may be that because we know that cytochrome P450 2D6 is not expressed to any appreciable extent in the fetal liver and nothing is really known about how long it takes in vivo for this pathway to turn on, it may just simply be that in a three-month old the P450 2D6 pathway hasn't turned on to a sufficient degree to convert enough codeine to morphine for there to be any

And so, his question is, well, is there any way that we can figure out when it

turns on? And we thought, well, that's a really interesting question. And so the literature at that time had several compounds that were being considered for effective or useful probes for measuring cytochrome P450 2D6 activity. Interestingly sparteine, and debrisoquine--debrisoquine is Diclomax, not available in this country, it was in Canada at the time and in Europe--were two of the compounds that were used to discover the cytochrome P450 2D6 genetic polymorphism, and for those of you who may not be familiar with this, about 7 percent of the Caucasian population, and I'm a proud member of that 7 percent, are genetically deficient in this particular pathway, and it was discovered using these two probes.

But another group had proposed dextromethorphan as a phenotyping probe and it seemed that of the candidate substrates for cytochrome P450 2D6, dextromethorphan was the only one that would really work to study this

particular question in children. And so let's go back to the characteristics of the phenotyping probe. In vitro studies show that approximately 83 percent of the cytochrome P450 2D6 dependent O-demethylation pathway, or 83 percent of this pathway is contributed by P450 2D6, and the particular metabolite is dextrorphan.

So, how good a probe, how quantitatively important is it? Well, in adults in whom the pathway is fully expressed, if you give a known inhibitor of cytochrome P450 2D6, it actually increases that metric area under the curve 40 fold, so that is a substantial increase in the product of concentration over time. And in fact, if you go to the extremes of the population in terms of genotype--so, I would be somebody who would be one of these PMs or poor metabolizers, I have no functional copies [of the 2D6 gene, and you compare the area under the curve with a systemic exposure in somebody

like me with somebody who has two good copies of the gene, there is actually an even more pronounced increase in systemic exposure, 150 fold, in this case.

So, cytochrome P450 2D6 is quantitatively important in the disposition of dextromethorphan. And so what we do is we use this metric of a urinary ratio of dextromethorphan to dextrorphan, the o-demethylated metabolite, in an interval of urine collection that in our studies is four hours, in some cases it's eight or 12 or even 24 hours. Now, this particular metric is counterintuitive because the larger the value, the lower the activity, so the lower the activity, the more of the numerator or the parent compound there will be, and the less of the metabolite that's formed. So, in the slides that I'm going to show you, high values are associated with low activity.

So, how did we do this study in children? What we did was to administer or

have administered a relatively low dose of dextromethorphan, 0.3 mgs per kilo, so this would be a 21 mg dose in your typical 70 kg adult, and these phenotyping visits were coordinated with Well Baby visits at two weeks, one month, two months, four months, six months, twelve months of age. So, one of the intangible benefits of the study was that we were contacting parents, moms, to make sure that they showed up for their Well Baby visits.

The protocol involved administering this relatively low dose of dextromethorphan after the evening feed. Our reasoning here was that if the infants were relatively unable to break down this dose of drug, that the primary side effect that we would see would be drowsiness, and that may not be all that disconcerting to mom after the last evening feed. The protocol involved overnight collection of urine, and we had to find non-gel based diapers from which we could recover the urine, and when mom brought back the wet and

dirty diapers--this was a real life study--we gave mom, in return, a case of dry diapers and so that was the incentive for the study. And I think at the time the cost of a case of dry diapers to us was somewhere in the \$13 to \$16 range depending on the size of the diaper, but it had a street value of around \$65 if you were to buy, you know, six toddler-size packages of diapers.

So, once we had the diapers in hand, we squeezed the urine from the diapers and measured dextromethorphan, the parent compound, and the metabolites produced by the body. The one of interest is this dextrorphan, but there are two others, 3MM and 3HM that are also formed.

These are the data, and I'm going to be running out of time, so let's walk through this slide. On the Y-axis is this ratio of the parent compound to the metabolite, so these high values are low activity and these extremely low values are high activity. And

you'll see that this is a log scale because we're covering one, two, a little more than three orders of magnitude. So, at two weeks of age, the variability that we saw in this population of children 147 infants at two weeks of age, we saw around three orders of magnitude in this metabolite ratio. Interestingly, at 12 months, we saw the same amount of variability.

In this part of the figure, it turns out that while we have--most people have two copies of the gene, there are some individuals that have more than two copies of the gene, we're not going to go into that today, but the different variant forms of the gene that are present in the population can have anywhere from no activity--my two copies have zero activity--or they can have sort of normal reference activity. And it turns out that you can go through and you can sort of assign a qualitative measure as to how much activity a particular version of this gene may have, and when you do that, you see that as the expected

activity associated with a particular version of the gene increases, this ratio decreases just as we would expect, and in fact that relationship is no different at two weeks or at 12 months of age. So, the conclusion from this study would be that even at two weeks of age, there is sufficient 2D6--cytochrome P450 2D6 activity that we can measure it, and there is sufficient--that most of the variability that we see at that age is related to genetic variation and not over the first year of life development.

So, genetic variation is more important to the population variability of a compound that is metabolized by this pathway than development, and that really doesn't change. We have continued this study over the first five years of life and it really doesn't change. Most of the variability that we're going to see in the population is due to differences in the gene and not due to age.

So, what application does this have?

Well, we've presented some of these data in a similar forum a couple years ago looking at the issue of cough and cold remedies, and I want to make sure that I have time to cover some of the other pathways, so the point I'd like to make here is that because we know that genetic variation is an important component of overall variability, one can actually use that information to design a study that would capture, pretty much, the amount of variability that one would expect in a population of children at a particular age or developmental stage, simply by screening the population for genotype and then selecting from the extremes of genotype, perhaps, let's say a half a dozen poor metabolizers and a half a dozen extensive metabolizers individuals with two or more copies of the gene, and looking at the difference in exposure between those two groups to get an idea of how important that genetic variation is.

So, let's just look at some of the

other pathways. Members of the panel will have in their materials provided to them a review article by Saskia de Wildt, Shinya Ito, and Gideon Koren, and that is a very, very, very good overview of issues related to phenotyping of cytochrome P450 3A4.

It turns out that when you look at the data, that ontogeny, or developmental changes, are actually much more important than genetic variation, but there's also another little twist to the tale and that is that cytochrome P450 3A4 is highly expressed in the gut and the liver and depending on the probe that you use and depending on the route by which that probe is administered, you can infer information on one or the other or both of those sites of CYP3A4 expression.

That review also goes through more of the details in terms of how these studies are conducted. Generally speaking, we're looking at pharmacokinetic type data to infer the activity of this particular pathway in

children. There is no one specific timed blood sampling point that can give you information on the pathway, and there are no metabolite ratios equivalent to dextromethorphan in urine that are useful either.

So, there are some real disadvantages for children here and particularly for healthy children, that would preclude the use of this as a phenotyping probe for healthy children, and those would be the need for multiple sampling times and the likely consequence of sedation.

Now, we can still get some information on the ontogeny of cytochrome P450 3A4 phenotype, and historically, these have been derived from either pharmacokinetic studies or therapeutic drug monitoring studies of particular medications and carbamazepine or Tegretol is an example of these types of studies.

So, I've tried to keep the structures to a minimum. This is dextromethorphan and

grayed out here is dextrorphan, but just the 2D6 pathway involves the loss of this particular methyl group. But it turns out that even though in adults this particular metabolite, dextrorphan, is about 70 percent of what we will recover in a collection interval, 30 percent comes from this particular metabolite, 3-Hydroxymorphinan, that lacks both the 2D6-dependent reaction and it also lacks a methyl group on this nitrogen that is likely lost here by this cytochrome P453A group of enzymes.

So, what I'm going to show you is how we can infer some information regarding the 3A4 pathway from this particular metabolite. This is, again, the same study, we were just measuring a different metabolite and what we've done here is we've said, okay, what proportion of all of the dextromethorphan and its breakdown products in the body are accounted for by that 3-Hydroxymorphinan metabolite, and what you can see is it goes from less than 20

percent at two weeks of age to approaching 60 percent at one-year of age, and for reference, this is the distribution that you would see, although not as broad as this, but a 70/30 split is what you see in adults.

So, this pathway is kicking in to a much greater extent and what we think is going on here--and this is likely reflecting the ontogeny of gut CYP3A4 in that this is a relatively--the dose--the concentration that the gut sees is pretty high because the drug is administered orally and we think that that gut 3A is what is contributing to the formation of that N-demethylated metabolite and, in fact, what limited data there are in vitro implies that there is a similar process that has been characterized using techniques to look at both the amount of CYP3A4 protein in the intestine at different ages here, and also a measure of activity, the formation of 6-hydroxy testosterone, which is a 3A4 dependent step.

So, what we see in vivo looks like it

probably is reflecting the ontogeny of the oral barrier of CYP3A4 substrates at the level of the intestine.

So, I'm going to go through quickly 2C19. Omeprazole is one of the prototypical substrates that have been used. This particular pathway was identified using a substrate--or a compound called mephenytoin that's no longer used. Mephenytoin is associated with a relatively high risk of hepatotoxicity so it's not clinically used anymore.

The use of omeprazole involves either a--most commonly a plasma sample obtained two to three hours after a dose. This is the adult protocol. Omeprazole is subject to biotransformation by two pathways but cytochrome P450 2C19 appears to be quantitatively important on the base of, for example, pharmacokinetic studies conducted in individuals who lack the pathway and those who have two good copies of the gene.

We have done--looked at some pharmacokinetic data and raised the question that maybe this is not the best substrate for 2C19 in children. I'll go through this relatively quickly because I'm approaching having gone over time. This is to show that CYP2C19 is one of these genes that is expressed, to some extent, in fetal liver. There is an increase in activity based on in vitro data over the first five months of life, and then there is a lot of variability here that looks very much like the variability that we see with cytochrome P450 2D6, that is, this is pretty much a flat line. Most of the differences in this direction, up and down, which would be consistent with genetic variation contributing to that variability.

These are some pharmacokinetic data from pantoprazole, another proton pump inhibitor, from a colleague, Bob Ward, and his group from the University of Utah, and they did three different studies of pantoprazole, which

turns out, in my opinion, to be a better marker of cytochrome P450 2C19 activity, but here is this issue of ontogeny. So, over the early--in the early post-natal period it's a straight line, there is no change with increasing post-natal age, and in fact circled, it may be difficult for you to see at the back, these two triangles are individuals who have two non-active forms of the P450 2C19 gene. And the purpose of this slide is to show you that their activity is on the low end of this clearance metric, but they are largely indistinguishable from the other members of the group.

Over here, extending the post-natal age up to 25 weeks, we are now maybe starting to see that the genetically deficient individuals separate out from the rest of the population, and then when you look at older children and pre-adolescents and adolescents, there is a somewhat decrease in activity over time with this clearance metric that takes into consideration changes in bioavailability or the

effect of bioavailability. Twenty-two percent of the variability in this clearance can be accounted for age over this range.

So, when you put it all together, you see that there is a little bit of a different picture. With 2D6 we said genetic variation, much more important than development almost right out of the gate, at least as early as we can measure, but here there look to be periods where ontogeny is important and then periods where genetic variation is probably important.

So, the reason I think pantoprazole may be a better probe is this particular study. This was a pharmacokinetic study of pantoprazole conducted within the NICHD funded network of pediatric pharmacology research units and both pantoprazole and omeprazole were studied by protocols within the network, and we did the genotyping for cytochrome P450 2C19 a few years after the studies were completed. Our question in looking at the genotype/phenotype relationship was actually

the activity of this *17 allele, this particular version of this 2C19 gene, that is associated with an increase in activity over the so-called normal version of the gene, and what we found was that whereas individuals who have two bad copies or zero functional copies of the gene have very high systemic exposure, this product of concentration over time, those individuals who have two good copies or one good copy and the active copy, have very low exposure, so that means the drug is being metabolized very rapidly and not very much of it is getting into or staying in the system.

On the other hand, with omeprazole this relationship was very erratic and, in fact, if you use a hybrid constant, the elimination rate constant, so here higher values are associated with more rapid elimination from the body, we see this sort of gene dose effect with pantoprazole but not with omeprazole. And so this is not something that we would have predicted from adult experience.

There is a very good gene dose relationship with omeprazole in adults. Why we didn't see it in adults, we can speculate--or, in children, we can speculate, but before we go too far with that I would say we would need to replicate these studies to make sure that this is indeed the case, but this does raise the possibility that not all acceptable phenotyping probes in adults may be equally informative in children.

Other pathways, 2C9, I've talked about this a little bit. Basically this is a little bit more difficult to do because none of the substrates that are available here would be a very easy sell in a pediatric population. Tolbutamide is probably the best in terms of being a pure 2C9 phenotyping probe, but you run the risk of hypoglycemia when using that even as a single dose phenotyping probe. And losartan is kind of interesting in that you can see these changes in AUC clearance with different CYP2C9 genotypes, but you don't see a

dramatic increase in exposure with inhibitors, and so that paradox makes you wonder what it is that you're really measuring if you're using losartan as a 2C9 probe.

So, to wrap up, and I apologize for taking more than my allotted time, phenotyping studies are important in children because we really need to understand how development contributes to variability in that does exposure response relationship, and that is ultimately what we want to get at. Before we do a clinical study in a child, we want to make sure that the dose that we are going to administer is going to have a reasonable chance of being effective.

And so, because variability comes from development, the whole concept of variability has an added dimension in children relative to adults, the variability is more complex because we have to take into consideration this developmental factor. What this means clinically is that we may be at risk for

concentration-dependent toxicities if we administer what we think is a normal dose but the primary pathway to get rid of that medication is not fully expressed.

On the other hand, we have these suggestions that there might be periods in development where children get rid of medications more efficiently than adults and so to extrapolate a dose from an adult to a child or a population where clearance is enhanced, if you will, runs the risk of not having sufficiently high concentrations to elicit a therapeutic--beneficial therapeutic response. So, for 2D6 the phenotyping studies tell us that genetic variation is more important than development and we can use that to design studies.

For 3A4 the available ontogeny data tell us exactly the opposite--that development seems to be more important even though we don't understand exactly why. And for 2C19 it looks like it's a combination of the two.

The issues are that most of the phenotyping probes that are available based on adult experience are not necessarily appropriate for use in kids and one of these would be safety concerns. The other concept that I would like to bring to your attention is this issue of a fixed dose, and in adults almost all phenotyping protocols will use a fixed dose, and this is probably among the least useful strategies for conducting phenotyping study in kids.

And I've just given you one little example here of why that is and that is if you give a 10 mg dose to a 20 kg child, so that's a dose of .5 mg/kg, and you give a fixed dose to a 30 kg child, and that's not unreasonable in a certain age range to have that range of body weights, while that difference in dose 0.5 mg to 0.33 mg may not seem all that big a deal to adults, it really does represent a 50 percent increase in dose for the child who's getting 0.5 mg/kg. So, 0.5 divided by 0.33 is 150

basically, and I would refer anybody who is interested into how using fixed doses in a pediatric protocol can totally obscure the information, Danny Benjamin and Jennifer Li did a study of failures, failures of pediatric antihypertensive studies and one of their best examples is a protocol involving a fixed dose of amlodipine in a high dose and low dose format and how the dose effect relationship was totally absent when the data were analyzed in the high dose versus the low dose group, but when you converted all the doses to a mg/kg dose, the effect on blood pressure was apparent.

Unfortunately, the information did not make its way into the label because that's not the way the study was designed.

So the questions to be addressed are things like, what is an appropriate dose for an approved compound? So, the use of low therapeutic or sub therapeutic doses. And I've added this--I added this one this morning, the

next one this morning. Is there such thing as a safe dose for compounds that are approved for adults but not yet approved for use in children? And then I would like to raise the issue of the utility of phenotyping data in healthy children mostly because it is hard to know when a disease--alterations in a disease state really represent a deviation from normal if there is no reference with which to compared the data, and there is also this issue of being able to establish what is normal variability because what we find, especially in the first three months of life, that variability is considerably greater in that period of time than at later periods of time.

And so, again, I'm revisiting this issue of the control group. Again, it's important for addressing the effect of disease state, but then one needs to address the issues of what constitutes a valid control group.

So, the way that we think through these now is to look at preclinical data, try

to find out what are the important pathways for drug disposition within what data are available on the developmental profile, what data are available regarding functionally relevant allelic variations, and how does genetic difference effect whether a pathway comes on quickly or more delayed, but especially in the context of children, we need to bear in mind that a lot of these so-called drug metabolism pathways also play an important role in the-- either biosynthesis or the catabolism of compounds that are important for growth and development, and this may have implications for adverse drug reactions.

So, with that, again, my apologies for taking more than my allotted time. Skip, I don't know how you want to handle questions or whether you just want to move on.

CHAIRMAN BOTKIN: Yeah, I think--thank you very much for an excellent presentation. We're a little bit over time but I think important to take probably five minutes or so

for some questions from our panel here.

DR. GLANTZ: So, have these studies led to changes in clinical care?

DR. LEEDER: I would say no. The ones that we have conducted, no, and in fact, what I didn't go over are the limitations of using the metabolite ratio, for example, the dextromethorphan study.

We cannot use that to infer the clearance of a compound just yet. They only tell us how to design the study to look at that parameter, and so the reason for that is that the metabolic ratio--I made a point of showing that there are three orders of magnitude, a thousand fold range in the metabolite ratio, that is a function of, you know, the numerator or the denominator changing in size.

We do not see a thousand fold range in either area under the curve values or clearance values in a population, so we need to be really important to say we cannot use this information to infer the clearance of a compound. The best

way to study the clearance of a specific compound would be to--would be a pharmacogenetic aided study design in our opinion.

CHAIRMAN BOTKIN: Norm?

DR. FOST: On one of your earlier slides, the one that's called "conceptual representation," it looks like once children get to be four or five, for most of the compounds you study it's sort of the same--there's not much value--not much difference between children and adults. Is that correct? Am I reading that there?

DR. LEEDER: The easiest answer for me is we don't know. That's just a cartoon, that was just me with an illustrator program drawing a bunch of curves. For a lot of things we don't know. Cytochrome P450--so, a compound like Tegretol, if you look at therapeutic drug monitoring data, it looks like--cyclosporine is another compound--it looks like children in that age range require a higher mg/kg dose to

achieve the same target concentrations and people will argue that, you know, that's an artifact of correcting clearance or dose for body weight rather than something like body surface area.

So, it's really hard to say. What we do know is that, you know, the dose, the mg/kg doses do decline with age. Why that is, whether it flattens out for all pathways, we don't know. The other thing that makes this a little bit more difficult is that we try to use phenotyping probes or look at this relationship in compounds that are highly dependent upon a single pathway for their elimination. A lot of compounds that are being developed now are cleared by multiple P450s to minimize the impact of drug-drug interactions and allelic variation. So, it's hard to say what that profile is going to look like for a lot of compounds. Hopefully because of that it will be relatively flat.

DR. FOST: Can I just ask my question

in a different way? Outside of infancy, outside of the first, let's say, year or two of life, how many examples are there of drugs in which there's been serious toxicity in children, not due to genetic variation, but due to developmental variation? How many examples are there in which if we relied on adolescent data we would have--if we relied on adolescent studies we would go seriously awry for a five-year old? How many examples are there of that? A lot? A few? One? Twenty?

DR. LEEDER: I don't know. My gut reaction is not very many. My concern would be more at the other end of the spectrum is how many times have we--are we under dosing children or taking longer to get to where we need to be because we haven't adequately characterized how well kids get rid of medications.

And it's important to kind of think of why it is that we have these pathways, why they turn on in gut and liver after birth, and I

would argue that these are the first lines of defense against foreign compounds that we take in as the--as part of our need for calories, food, after birth, and the timing of a lot of these things that are highly expressed in the gut intestinal villus and in the liver are also the things that basically prevent us from the products of plant-animal warfare and, you know, small molecular weight compounds administered with therapeutic content fall into that category as well.

So, I think the issue is more how many--is related to running the risk of not getting where we need to be therapeutically because we don't understand this. One thing that comes to mind is Tacrolimus in African-Americans. The upper--the guideline, the upper limit of Tacrolimus dose was basically derived from Caucasian populations. It turns out that African and African-American populations have a high frequency of cytochrome P450 3A5 functional gene, functional protein. That

means that 90 percent of the population has at least one good copy of the gene as opposed to-- I forget what it is, maybe 20 percent of the Caucasian population--and so we have had situations at our institution where the nephrologists have gone to the highest allowable or recommended dose of Tacrolimus and not been able to achieve detectable concentrations and it turned out that the patient who was our signature case of this had two good copies of the gene and required considerably higher doses of the medication.

That's a not a developmental issue, but it just shows that the relative paucity of data in children can have some impacts and I think it would be more likely to be on the clinical side--on the effectiveness side rather than on the toxicity side, but I don't have any hard data to provide to you. Perhaps the clinicians would have more examples than I do.

CHAIRMAN BOTKIN: Loretta?

DR. KOPLEMAN: About how many subjects

are in these studies?

DR. LEEDER: The phenotyping studies that I showed, in the first year of life we had 147 children at two weeks of age and I think 112 individuals we have at 12 months of age. We continued that on in the first five years of life and on average there were 60 kids at each of the time points, but only a subset of those do we have a phenotyping measure at each of the visits.

So, longitudinal design, I didn't go into longitudinal versus cross-sectional designs. Longitudinal designs give us a better idea of the actual developmental profile. So, that's why we prefer longitudinal studies rather than cross-sectional.

CHAIRMAN BOTKIN: Thank you. Steve?

DR. JOFFE: So, when asked about how this kind of information affected clinical care you said you didn't think there were many examples to date. I'm wondering if you might sketch out a vision of how, you know, whether

it's 10 years or 20 years from now, once we have the ability to easily and routinely measure, you know, the genetic variation in each individual and be able to pharmacogenetically tailor and assuming we can get to the day where we understand fairly well the developmental trajectory across the ages of childhood for each of these enzymes, how--a vision of how personalized medicine, personalized drug dosing might look once we have both those sets of information?

DR. LEEDER: Yes, that's a really excellent question. So, the way that we are addressing that at our institution is embedding--actually, we're embedding pediatric sub-specialists into our clinical pharmacology program and they generally have a disease or drug or combination of drugs that they're very much interested in.

The first step that we take is trying to capture the population, characterize the population variability. So, one example is the

rheumatologist that I mentioned to you who was very much interested in why roughly 55 percent of her kids that she was treating with methotrexate didn't respond to the medication. A secondary interest was those who had gut and liver toxicity.

The first thing we did was to say, well, you know, how much variability is there in her population of juvenile idiopathic arthritis kids in terms of methotrexate polyglutamation, because this was something that was of interest to the adult world, and then our next question was how much of that variability is due to development, how much of that is related to genetic variation and folate pathway genes, and then from there we go, okay, well, what genetic variations are responsible for the variation, with the intent of perhaps trying to identify those kids at risk for lack of effect before they get the drugs.

So, that's kind of--the vision that we have is where possible, trying to get real life

data from a clinical population and then using that preliminary set of data where we explore the variation and sources of variation to design the study that--a prospective study, that would be a little bit more rigorous in terms of determining how important those individual factors are prospectively to make a decision as to whether they should be incorporated into a personalized medicine strategy or not.

Does that answer your question?

That's our vision. I mean, there are many different ways of doing it. That's the way that we're approaching it.

CHAIRMAN BOTKIN: One more question here, Alex?

DR. RAKOWSKY: Thank you, Dr. Leeder, for the nice presentation. Sorry for having my back to you here.

Your study--your presentation really focused on traditional drugs. What's the field look like as far as understanding

pharmacokinetics of biologically active agents, for example, month-long antibodies or exon skipping agents, interfering RNA, et cetera. I mean, how applicable is some of this work to how people metabolize those agents?

DR. LEEDER: Oh, I would say it's equally applicable and not enough people are asking that question.

Particularly in terms of biologicals, I would say that any time you see variability it begs the question of how much variability is there and what are the sources of that variability and which of those sources of variability do we have control over in terms of trying to optimize a therapeutic strategy. We have some unpublished data that was actually presented at the American Society of Clinical Pharmacology and Therapeutics that looked at an association sort of basal energy expenditure and the pharmacokinetics of clearance of a biological, and I can't remember what one it was, I wasn't directly involved in the study,

so I think that these principles are equally applicable to anything, any sort of therapeutic modality that could be used in children or adults. And the question is just figuring out how you're going to approach it.

CHAIRMAN BOTKIN: One more question, Dr. Dasarathy?

DR. DASARATHY: Thank you so much for the wonderful talk. I had an extension on the questions that were asked about the clinical applications, and from what I understand from the different graphs that you showed, especially for ontogeny, I am still not clear how doing these testings would really help in prescribing practices compared to actual measurements of doses, and I'll tell you why I ask this.

When I'm on service, every time we check levels, cell CYP levels, we keep checking levels, and irrespective of what the genetic testing will show, our prescribing practice is going to be based on what we see in the plasma

concentrations. And to me it appears that it's even more relevant when there is a progressive change in expression of the activity of the metabolizing enzymes. In that situation, unless we keep doing these genetic testings, and even if we do that, it doesn't necessarily translate into clinical practice.

So, I'm still not sure how we will use this towards deciding prescribing practices.

DR. LEEDER: There are--boy, there are a number of ways that--a number of comments I would like to make in response to that question. I'll try to keep it targeted.

The application of pharamcogenetics to children is no different than being applied to adults in the sense that we need to make sure that everything is kept in context and that the benefits of what information genetic assessment--the information that it provides how it can be used.

In the case of Tacrolimus and its use in pediatric transplant, I would say that given

what we know now, the value of a CYP3A5 genotype would be to identify those individuals who are going to have two copies of the gene and might have higher than anticipated clearance so that you don't necessarily start off with Caucasian-derived dosing guidelines and strategies for African-Americans or anybody else. I mean, you can have Caucasians who have two functional alleles as well.

So, I mean, you can't make these calls based on sort of reported race, you need to make it based on genotype.

It helps in many cases with the starting dose, to give you an idea of where you ought to start, but it doesn't tell you, necessarily, where you're going to go, especially if there's auto induction or if there is going to be inhibition or something else that changes over time, so I can't give you a blanket statement of when it's effective and when it's not going to be effective, but we need to make sure that we understand the

limitations and what information it does provide and what information it doesn't. And it's probably going to have to be done on a case-by-case basis.

CHAIRMAN BOTKIN: Real quick with Dr. Rosenthal, last question.

DR. ROSENTHAL: So, on this issue of variability and drug response, I have a question that may not be answerable, but I'm going to float it anyway. So, I'm thinking about adverse events, adverse effects of drugs, and, you know, I believe that this represents probably an extreme end of the spectrum of drug response and probably the different areas of variability that you identified earlier, you know, ontogeny, genetic variability, disease states, environmental influences, can also influence the occurrence of the extreme forms of response, the negative response to drugs.

I'm wondering if you have a sense for how, in the extreme case, the variability and response would be partitioned across those kind

of, you know, general categories of influence as--and I'm not sure whether there's any data that comes to mind that would help us to understand that, but is--which of those four elements do you think is the predominant effector of adverse drug events? And then how might those fall out?

DR. LEEDER: By the four factors do you mean absorption, distribution--

DR. ROSENTHAL: No, I'm thinking more about developmental patterns, genetic variability, environmental influences, and disease states, and, you know, granted that things like environmental influences and disease states, those are complicated issues in and of themselves that you haven't really addressed, but--or that we haven't gone into in detail, but what's your general sense for the importance of these different opportunities for variability?

DR. LEEDER: It is a difficult--so, genetic variation, in its really rudimentary

state right now if we just focus on genetic variation and drug metabolizing enzymes, I think we can predict concentration-dependent toxicities. What I find a little bit--and so that might be a little bit easier to predict.

The kinds of things that intrigue me are things like why are children under the age of two receiving concurrent enzyme-inducing anti-epileptics at such dramatically increased risk of valproate hepatotoxicity. And that's not something that we're necessarily going to get out with a drug biotransformation phenotype.

One of the intriguing areas associated with that that might get at the toxicity sort of thing is we are kind of turning our attention to the possibility that there might be a developmental or an ontogeny of mitochondrial function, for example. If you think about it children who are growing and developing, who are changing a lot, have probably markedly different energy expenditures

and requirements than senescing adults do, so is there a--is there, number one, a developmental--is there a trajectory of some sort of mitochondrial function?

And, number two, are there uniquely vulnerable periods within that trajectory for challenges like a medium chain fatty acid load, like what valproate really is. And number three, is there a particular genetic makeup that does not allow someone in the vulnerable period of challenge to adapt to that medium chain fatty acid load as effectively as another genetic makeup?

So, I'm not really--I don't think I'm really addressing the question. I think the question really points to the fact that we really don't know what underlies a lot of the issues related to drug effect and drug safety that are unique or occur at higher frequency in pediatric populations and I participated in a sort of an NICHD vision workshop a month or two ago and one of the suggestions by the group

that I was involved with was we really need to understand, not just in kids, but right from-- in pregnancy through the continuum to adulthood, an ontogeny of a lot of these normal pathways that are either part of the developmental process or physiological changes associated with things that are not experienced in 70 kg white males.

So, my plug is not really answering your question but I think we could--placed in a room for a sufficient period of time, I think a lot of people could come up with issues of developmental--developmentally related variability that warrant investigation.

CHAIRMAN BOTKIN: Dr. Leeder, thanks again. We'll have an opportunity to ask more questions as our discussion period opens up a little bit later this morning. Dr. Nelson?

DR. NELSON: Let me just get this up. So, I think that was a wonderful introduction to the scientific issues and I'm sure a lot of the--a lot more questions that will be explored

as you get into the details.

What I'd like to do now is just provide a general overview of an ethical framework based on 21 CFR 50 subpart D are additional protections for children, that will kind of give you that side of the set of issues as you begin to get into the questions that we're going to present.

The way we have it scheduled is I'll do that general overview, then there will be a break and Michelle can then present the specific questions for the committee to consider, which you also have in your folders for presentation.

Let me start by emphasizing the view that the performance of research in children is a moral imperative. Now, I realize some of you might trod out the quote by Hans Jonas that, in fact, "research is optional", but I think that approach in pediatrics has led to historically to us not having products that are demonstrated to be both safe and effective in children.

This is a quote taken from a statement by the American Academy of Pediatrics, and I'll just point out the last comment about it, "It's morally imperative, given some of this variability that we've been discussed, to formally study drugs in children so that they have access to appropriate, existing and new therapeutic agents."

So, we've moved over the last 15 years from a view that we must protect children from research to a view that we must protect children through research. But recognizing that, we then have a professional obligation, both as clinicians, regulators, and as ethicists, to ensure that there's adequate data to support the safe and effective use of drugs, but this need for data also means that we need to be sure that the protocols that children are thus enrolled in are both scientifically necessary and ethically sound, both sides of that equation.

Children are widely considered to be a

vulnerable population who, as research participants, require additional or special protections, which gives us our subpart D, which I will then introduce not all of it, but those components that I believe are important to the discussion today.

So, this will be what I'll present, the introduction, then I'll focus on two key concepts briefly, look at what I'm calling the higher risk pathway which, to some extent, is not applicable to the exploratory IND studies, the low-risk pathway, and then some final comments on risk assessment.

So, first, on the basic ethical framework. So, there's four principles, these are the first three, the first is that children should only be enrolled in a clinical trial if the scientific and/or public health objectives cannot be met through enrolling subjects who can provided informed consent personally, in other words, adults. The second principle is absent a prospect of direct therapeutic benefit

to the children enrolled in a clinical trial, the risks to which those children would be exposed must be low. Now, the language we use in subpart D is "minimal risk" and "minor increase over minimal" risk, but I'm using low-risk here to encompass those two. In other words, knowledge does not justify more than low-risk as it might in enrolling adults.

Third, children should not be placed at a disadvantage after being enrolled in a clinical trial either through exposure to excessive risks or by failing to get necessary healthcare, and I'll show you how these play out.

So, the first principle of scientific necessity, the issue there is based on the principle of equitable selection. Now, if you look back at the National Commission's discussion in the 1970s of equitable selection, they specifically were talking in the context of pediatrics about subjects who are capable of informed consent should be enrolled prior to

children. In other words, if you can answer the scientific question--now, in this context, I think, obviously the presentation by Steve points out that many of the scientific questions that need to be addressed cannot be answered in this context by studying adults, but we would not enroll children unless it's essential to get those answers and there's no other option.

I'll point out that equitable selection--we normally think of gender equity and ethnicity and race equity, but this is how it was discussed by the National Commission back in the 1970s in the context of the Report on Pediatrics.

Now having said this, equitable selection does not imply that adult studies need to be completed before beginning pediatric studies. If we took that position, we would always be doing pediatric research when a product is available on the market and is then prone to being used off-label, and that may

well be an impediment to research as well as exposing children to products that have not been demonstrated to be safe and effective.

The amount of data we need is sufficient data to be able to move forward either under a situation where we have proof of concept on prospect of direct benefit, which justifies exposure to those risks, or where we have sufficient data to conclude that the risks of the intervention are no more than a minor increase over minimal risk, and these are the higher risk pathway and the low-risk pathway, which you'll see me develop further through the presentation.

So, adults should be enrolled if they're pertinent, prior to adolescents, younger children, to obtain data in support of this judgment. Once we have that data, though, we can then begin to move forward.

Now, the general justification of research in--for both adult and pediatric subjects is that the risks to the subjects must

be reasonable in relationship to anticipated benefits if any to the subjects and the importance of the knowledge that may be expected to result. So, if you look carefully at the logic of that sentence, it means you can, in fact, for adults, justify risk in relationship to knowledge, because there may be no benefit. We then add the additional protections to children that modifies this in two ways.

The first modification is that if there is no prospect of direct benefit, the risks must be restricted to either minimal risk or a minor increase over minimal risk and that's what I will be referring to as the low-risk pathway. Or if, in fact, the risks are greater than that level or if there is some prospect of direct benefit, the risks must be justified by that anticipated direct benefit and the balance of risk and benefit must be comparable to available alternatives. So, as you notice, this is principle two and principle

three as reflected in our regulations.

Now, the fourth principle is that we should have parental permission and child assent, if appropriate. I'm not really going to speak to that issue any further, but I wanted to point out that there is, in fact, a fourth principle behind this, and this is what gives us our subpart D protections and this is simply a listing of the sections of 21 CFR 50 subpart D that encompass these protections with the four categories of research--minimal risk, greater than minimal risk, prospect of direct benefit, no prospect of direct benefit but a minor increase over minimal risk that would yield generalizable knowledge, and then the 50.54 category, which is--you know, may be on the table, depending on your discussion, but is the protocol that was referred but then withdrawn was that the healthy controls may have fit under that, and then of course parental permission/child assent.

So, as I mentioned, with this context,

the challenge here is to establish sufficient scientific data using either preclinical animal models or adult human clinical trials to conclude either that we have enough data to move forward under the low-risk pathway absent a sufficient prospect of direct benefit if we can determine that there is an acceptably low-risk, or that we have data showing proof of concept that might justify the administration of a investigational product to a child where we have sufficient prospect of direct benefit to justify those higher risks, and that's the low-risk and the high-risk pathway.

Now, these two pathways need to be distinguished. An important concept there is what's often referred to as component analysis, and this is a quote from the National Commission's Report on Research Involving Children from 1978 which points out, "When you determine the overall acceptability of the research, the protocol itself may include components that either do or do not offer a

prospect of direct benefit. You need to evaluate those individually as well as collectively."

And the intent here is to avoid what has been called the fallacy of the package deal which is you can take high-risk, non-beneficial interventions, put them in a protocol, and if you then package them with enough items that may offer a prospect of direct benefit, you're then justifying those high-risk items that offer no benefit by this other packaged benefit. That may result in unfortunate results such as including necessary healthcare in a protocol that then would be used to justify a high-risk intervention with no benefit inappropriately.

So, what do you need to do? You just need to break it down. In the interest of time I won't go through the slide, but you say, you know, does it or does it not involve direct benefit, and then assess each one of those on their own merits.

So, the key concept here that divides these two pathways is obviously this notion of prospect of direct benefit, and here is a few thoughts to try and lay out what that might mean.

So, the first point is that it's direct, meaning it's my benefit, not your benefit. If you're talking about a direct benefit to me, it's my benefit and not your benefit. You may benefit from the knowledge, for example, of something that you do to me, but do I benefit from that concretely? The idea also is that it results from the research intervention being studied and not from other clinical interventions in the protocol, and we often modify this word by clinical to indicate that we're, in fact, talking about clinical benefits, since strictly speaking, if you paid me to be in a research protocol, that is a direct benefit to me, but we often--we don't use that as a justification for the intervention.

The other point is that it's based on the structure, and what I mean by that is it's not so much intentionality, but it's something we can judge based on the data. What's the dose? What's the duration? What's the method of administration? What's the data in support of the possibility that that intervention has a prospect of direct benefit? For you philosophers, we could go to the Doctrine of Double Effect and intentionality, et cetera, on this, but we don't have to go there.

The other point is that the necessary level of evidence to support this is less than that required to establish efficacy, because obviously if we required efficacy data before we start a research protocol then it's a circular loop, we would never, ever do any research, so that's a simple point. And then whether or not the experimental intervention offers a prospect of direct benefit is a separate question from whether or not that prospect of direct benefit is of sufficient

probability, magnitude, and type, to justify the risks of the intervention given the overall clinical context, and this is a complex judgment that needs to be set within the context of the disease, et cetera, and for those of you who were at our meeting a couple of years ago on the prospect of direct benefit, I think this does draw on many of the ideas that were discussed at that meeting.

So, let's move now to exploratory IND studies. What makes them inappropriate for the high-risk pathway is they're designed with no therapeutic or diagnostic intent, so there is no prospect of direct benefit in those studies. It does involve very limited human exposure, it may have limited drug exposure in terms of the dose that's chosen or the duration. There may be a small number of subjects, but obviously the one that Steve reported on had a fairly large number of subjects, in the 140 range, which I think would be actually a large study relative to many other phenotyping studies that

are, at least to my knowledge, published. They're often--they're conducted early in Phase 1, although I'll point out in pediatrics these categories often lose the classical meaning since the adult program could have been proceeding into Phase 2 and Phase 3 when we're beginning the pediatric program. So, it may be early development from a pediatric perspective, it could be fairly late in the adult program, but it's prior to traditional dose escalation, safety, and tolerance studies that ordinarily initiate a drug development program.

And for those--I'm taking this from the "FDA Guidance on Exploratory IND Studies" that was put out in January '06.

So, the objectives here are to determine whether a mechanism of action can be observed in humans, as you saw the scientific presentation. It may involve information on pharmacokinetics, it could help you select the most promising lead product from a group of candidates designed to interact with a

particular target based on pharmacokinetic or pharmacodynamic properties, it may help you explore products biodistribution, if you get into imaging studies which are not the subject of these sort of more metabolic and pharmacokinetic and pharmacogenomic studies, but are certainly part of potential exploratory IND studies.

Now, this is a direct quote taken from that guidance: "Because exploratory IND studies involve administering either sub-pharmacologic doses of a product or doses expected to produce a pharmacologic but not a toxic effect, the potential risk to human subjects is less than for a traditional Phase 1 study that, for example, seeks to establish a maximally tolerated dose. Because exploratory IND studies,"--and I've added this emphasis--actually, this emphasis is in the document as I recall--"because exploratory IND studies present fewer potential risks than do traditional Phase 1 studies that look for dose-

limiting toxicities. Such limited exploratory IND investigations in humans can be initiated with less or different preclinical support than is required for traditional IND studies."

Now there's a very important footnote in that guidance. "These types of studies would not be carried out in pediatric patients or in pregnant or lactating women."

We're here, really, to discuss, to some extent, that footnote and one of the questions that Steve put on his slide, which is something that I think I would love to hear the committee address, is the extent to which the safety information needs to be in hand to be able to initiate these kinds of studies in pediatrics. What's the extent of that information?

But the assumption here behind this is that in an exploratory IND study in adults there's a lower bar for doing preclinical safety and toxicology studies before you would move in to what would be a limited drug

exposure in humans, and the basic question is the extent to which that's appropriately considered in pediatrics.

So, applying subpart D, now, 21 CFR 50 subpart D applies to a clinical trial regardless of whether one child or 100 children are exposed to the experimental drug. This goes to the issue of a limited exposure. Regardless of whether we have 150 kids or 50 kids or 10 kids or 5 kids, we still need to decide that it can proceed based on subpart D. The risk is not limited by reducing the number of exposed subjects.

The other point is that the risks of drug exposure remain the same for each child enrolled in the clinical investigation. In other words, there is no more or less risk for Child 1 versus Child 100 unless, of course, you have the data from the other 99 that you can then evaluate to decide whether that risk has, in fact, changed, but if you--this is simple high school probability.

You flip a coin, it's going to come 50/50 each time. Regardless of how many times you've flipped it, it's still 50/50 each time you flip it.

So, the question is, given the lack of prospect to direct benefit, what are the conditions under which a pediatric exploratory IND study could proceed using the low-risk pathway in the context in which there is no prospect of direct benefit?

Now, the low-risk pathway may have limited applicability depending on the product because you need to have some estimate of the risk to be able to state with some degree of confidence that the risks are, in fact, low. It could be used for drugs if sufficient data exists to know that the risk of use is low. For example, over-the-counter cough and cold products and the use of dextromethorphan would be an example of that.

Just to lay out briefly some of the concepts behind that, the National Commission

defined minimal risk as "those risks normally encountered in the daily lives or in the routine medical or psychological examination of healthy children." The ethicists in the room, and maybe everyone else as well, recognizes that the phrase "of healthy children" was deleted from the current definition, yet I will say that most ethicists and U.S. federal panels, including SACHRP and the Institute of Medicine, agree with this limitation, in other words, argue that minimal risk should be interpreted in the context of the life of a normal, healthy child and not indexed, if you will, to the life of children who may be at greater risk based on environmental exposure or disease exposure, et cetera.

So, acknowledging this restricted definition--first of all, so the administration of experimental drug products is generally neither normal nor routine and thus is not minimal risk, although one of the questions before you, it'll be question two, is, to what

extent, if you're administering a sub therapeutic dose, does that conclusion change and under what circumstances?

So, by acknowledge this restricted definition of minimal risk, this is why the National Commission added a category of research presenting a minor increase over minimal risk, which is fairly unique to our regulatory structure when you actually look at the other regulatory frameworks around the world. So, what does this minor increase mean? Well, there's no definition in the regulations. These are quotes taken from the National Commission's discussion where they say that this is "supposed to be no significant threat", again, an interpretation of the word "significant" would be required.

"Given the promise of substantial future benefits", what does that mean in terms of substantial future benefits? You could justify a risk that's beyond minimal risk, but only slightly beyond and so you have these

terms that require some discussion. In addition, the interventions or procedures that must be a low-risk have to be limited to children with a disorder or condition absent a federal exception, and this is what resulted in the protocol referral which was withdrawn was because the control group of healthy children did not have a disorder or condition.

Here is just a list of referrals to remind you to date to this subcommittee under 5054. I'm not going to go through all of them but the bottom line is all of them, a common theme was the administration of intervention that presented a minor increase over minimal risk to children lacking a disorder or condition. That was the common theme of all four of these referrals.

So, how is a disorder or condition defined? There is no definition in the Federal research regulations. Here's one definition that's been proposed by the Institute of Medicine, there's some minor modifications of

this by the Secretary's Advisory Committee on Human Research Protection, but it basically says two things. One is, you either have some scientific or clinical evidence that the child has a disease. In other words, something is negatively affecting the child's health and well-being at that time. Or you have some scientific or clinical evidence that that child is at risk for developing a health problem in the future.

So, the key concept here is both-- either having a disease or being at risk for a disease, and being at risk for that disorder or disease.

Now, let me give you one quick example, pharmacokinetic studies of over-the-counter cough and cold products, the question came up--and this is in the public domain--as to whether you should be able to do these in healthy children since all children get colds. The feeling was, no. It's actually not true that all children get colds, if you actually

try to divide the population, if you're a single child living at home being homeschooled, the odds of you getting a cold in the first six years of life is pretty low. Evens out about the age of 14, but that's because you've gotten out into the population, so you could go back into the early literature and define some categories of risk that would establish a child who would be at risk for a cold, and these would be using frequency, crowding, or exposure.

I won't go into details, but these were based on data that were produced in the 1950s and '60s from basic epidemiologic studies, so an asymptomatic child could be at risk. Now, it's possible that that criteria would describe 80 percent of the pediatric population, but that's not the point. The point is you do the research in children that have a disorder or condition because, in fact, it's not considered minimal risk to give children a product that they, in fact, don't

need or are not at risk for that condition.

So, having discussed the low-risk pathway, let me just make some remarks on risk assessment. So, by definition, an exploratory IND study has to produce a measurable effect. You're either measuring in the urine or you're doing something, it's in the blood, you're doing plasma, something--PK, PD, receptor binding, enzyme inhibition. The question is, in assessing the risks of drug administration, can we usefully employ such concepts as microdose, pharmacological effect, sub therapeutic dose? In other words, how can we begin to draw distinctions that would allow us to sort of tease apart the risks of these different interventions?

Steve introduced one, which is, is it approved, for example, for pediatric use? Is that a distinction that we could use or not? What's the data in support of that?

And depending on the targeted effect, how much preclinical and human adult data are

needed to be able to assess these risks? And what I have here are just two quotes from the "FDA Guidance on Exploratory IND Studies" that support these questions around microdose studies which are intended to give you an effect, but not necessarily a pharmacological effect, show a change in the enzyme that you can measure in the urine, but not necessarily produce a blood pressure change or a change in level of consciousness or sedation, et cetera.

Now, so assuming that the administration of a single therapeutic dose of an experimental drug presented no more than a minor increase over minimal risk, could a sub therapeutic dose of that same drug be considered minimal risk? This is question two that you'll be addressing which Michelle will go through.

There are other moral issues, for example, commodification, that should be considered in assessing the acceptability of enrolling healthy children in experimental drug

studies. How should these issues be incorporated into an assessment of the ethical acceptability of such studies? That will be question three that Michelle will show you in more detail.

Now, when we define acceptable risks, one of the difficulties here is that the definition of risk as the product of probability times magnitude gives the misimpression that risk assessment is purely a quantitative exercise. If you go to the literature on risk assessment I think you'd understand that that's a simplistic view.

The disvalue of a harm or of that risk cannot be quantified to where a uniform or comparative standard can be established. Defining minimal risk by using as a reference either daily life or routine examinations runs the risk of reducing a moral evaluation through comparison of the factual risks. So, in other words, the fact that a risk occurs outside of the research setting does not make it morally

acceptable inside the research setting, and that's the problem we have.

One of the examples I might use, a few months ago I was watching the news and there was a special on parents who allow their kids to drive in rodeos of all-terrain vehicles. You know, I mean, we let parents do that. There's events that are organized by adults for parents to do that and they segued from that and the kids having a great time, six-year olds jumping these all-terrain vehicles over, you know, barriers and dirt and et cetera, and then they segue to that to the kid in the wheelchair that fell off and is at that point left paraplegic.

I would argue that that's probably not a daily life research risk, even though we allow parents to make that decision, that we would accept in a minimal risk research, so that's the basic argument there. But having said that, we're still left with the dilemma of deciding what's acceptable or not. Now, multiple factors are relevant to the moral

evaluation of risk--harmfulness of the event, the type of harm it represents, its probability of occurrence, the distribution of the risk, whether it's voluntarily assumed or involuntarily imposed, the context of the activity, and other factors, this is just meant to sort of explore it. And so, to some extent, pluralism in risk assessment may be a practical, theoretical, and moral necessity, even though there is a fair amount of criticism of variability in those assessments, but part of the--my desire to hear a discussion is how can we begin to get a sense of what's appropriate variability and inappropriate variability.

So, the broad topic for discussion here is exploratory IND studies do not offer a prospect of direct benefit given the use of sub therapeutic drug exposures. Then how do we assess the appropriateness of these studies within the ethical framework provided by 21 CFR 50 subpart D?

Thank you, and we'll actually present the more detailed questions later and whether, I guess, we can--Jeff, I'll leave it to you whether we take some questions now or do that after the break.

CHAIRMAN BOTKIN: Yeah. Thanks, Skip. And thanks for moving through that so efficiently. I do want to take a couple of questions at this point, but encourage folks to be concise.

Lainie?

DR. ROSS: I just have a quick question. Now that dextromethorphan and all of these cough medicines have been taken off being over-the-counter for children under the age of seven, how is that going to change our notion of its risks and benefits?

DR. NELSON: Well, first of all, I'm not sure that's a factually--dextromethorphan I have to check whether it's age two or age six, but I know the labeling has changed, but I think it's under two that it's--you know, that

it's not supposed to be used.

But the bottom line is, I mean, that's precisely how you should begin--you know, if that's a consideration around labeling, then that's a consideration you should put into the discussion. I mean, the issue is going to be, what are those considerations that one might bring to bear on deciding on the safety of these products that are used.

DR. ROSS: Well, I meant it in the more--so, going back to Dr. Leeder's study, could he have done that same study today given that we no longer "use" dextromethorphan in the two-week, two-month, six-month, 12-month, and the first six age groups that he included?

DR. NELSON: Well, I will say, I was an IRB chair of an institution that approved a study such as that. We did it as a minor increase over minimal risk and we argued that the children that were being enrolled less than a year had a developmental abnormality in cytochrome P450 enzymes and therefore had a

condition, and we put it under 50.53.

Now, we could--

DR. ROSS: You only knew that after the fact if they had--

DR. NELSON: Well, that was the hypothesis and there was some evidence in support of that. I mean, I'm just saying that we're getting into the content and that's precisely the questions that we've put before you to cogitate over.

CHAIRMAN BOTKIN: Yes, Dr. Zuppa?

DR. ZUPPA: Thank you both. So, it's kind of a question for both of you. Skip, going back to your slide, you say given a conservative limit of minor increase over minimal risk, promise of future benefits to children other than the subject does justify the research. Just in that context, speaking to this hypothetical protocol, the phenotyping studies that are done--I understand how they help to explain variability and the dose exposure, and to some extent, the exposure

response relationship.

Would they, in a specific disease state--so, say you do see a difference in probably more genetic expression in a disease state versus a non-disease state--would the outcome of that study obviate the need for future PK studies in that disease state? So, if you do see a difference--or, say, you don't see a difference in the expression of these genetic factors for metabolism, would they be used for dosing guidance for future Phase 1 studies or would they obviate the need? I think they're kind of tied together.

DR. LEEDER: Let me see if I understand the question. So, if one were to conduct a study in a disease state where one is--wishes to investigate the cytochrome P450 2D6 pathway and uses dextromethorphan, how well--would there be any need to conduct a PK study in strattera or atomoxetine, for example, that is another CYP2D6 substrate, or risperidone? Is that the question?

DR. ZUPPA: Correct. So, in the hypothetical protocol, we--the hypothesis is that there is a difference in expression of these genetic markers or--in the disease state. So, say you do find that out by doing this--comparing it to healthy controls. Are you--you see that there is no difference--would you feel comfortable saying, okay, now there's no difference, we can just go ahead with normal dosing and we don't need to do a Phase 1 study in this specific disease state?

DR. LEEDER: I don't know that I would go that far. I mean, we need to bear in mind that when we do a phenotyping study all we're really assessing is metabolism and I made the comment that for different--you know, different medications may have multiple, one or more, P450s contributing to them. But the other thing to remember is that a population of 100 people, even though studies done with, you know, a couple of microsomal preps in a preclinical evaluation doesn't capture the fact

that among the 100 of us in the room, all given the same CYP2D6 substrate, are going to have varying formation of not only the CYP2D6 metabolite, but the other metabolites, and that's because our compliment of hepatic P450s is going to be different.

Even if you had 100 people in whom cytochrome P450 is not polymorphically expressed, in some of us it may represent 5 percent of all of the P450s that are there, some of it might be 20 percent, some of it might be 2 percent, but the competing pathways, like cytochrome P450 3A4 might represent 60 percent and for others it might be 30 percent, so we can't--we have that degree of variability.

The other thing is, is that phenotyping studies like I described only measure drug biotransformation and we can't exclude the possibility that there aren't genetic or environmental or developmental differences in all of the other processes that

determine how much of what we take in by mouth or is given intravenously actually shows up in the system. So, I think you still have to do those PK studies to get the information that you need, it's just that you might design the study differently for 2D6 than you might for something that's primarily metabolized by 3A4 or something else.

DR. ZUPPA: So then, just as a follow up, I think tying back to that comment where future benefits to other children for minor increase above minimal risk actually speaks to the scientific merit of the protocol under review.

So, my--I don't know if I'm being clear in what I'm saying, but I think I the hypothetical protocol, again, I wonder if exposing these healthy children to the sub therapeutic doses is actually worth it. Is it going to answer a scientifically important question does not obviate the need for additional studies.

DR. LEEDER: Okay.

CHAIRMAN BOTKIN: All right, I had a question for Skip regarding your thoughts or what you think the history of thinking is on this issue and how it is we define prospect of direct benefit. And in those contexts where we're using, say, a single dose or a short course of medication for a chronic disease, even at therapeutic doses, thoughts on categorizing that sort of intervention as having the prospect of direct benefit?

Have we been clear with that question?

DR. NELSON: So, in other words, if we're doing a single dose study?

CHAIRMAN BOTKIN: Yeah, of an agent that would otherwise be therapeutic agent for a child with a condition. Under what circumstances would a single dose or a short course be considered as having a prospect of direct benefit?

DR. NELSON: Well, I think the devil would be in the details. I mean, if you're--to

continue the cough and cold analogy, let's take an eight-year old so that we're not dealing with Lainie's issue about the labeling. If you've got, you know, rhinorrhea and you're given a single dose of a decongestant, that may in fact offer benefit for the two or three hours after you have some--at a therapeutic dose of that product since that's administered on a PRN basis anyway.

So, you know, I wouldn't make a strong argument for that but it's theoretically possible that a single dose at a therapeutic level would in fact provide benefit for a symptomatic condition where a single dose would do that. If you're giving a single dose of an antibiotic, unless it's a--I know there was some--you know, a urinary tract infection where a high dose of an antibiotic in a single dose might clear it, et cetera, we could debate that, but it's unusual where a single dose of a product would be considered a sufficient therapeutic benefit.

A vaccine would be, I mean, there's a lot of examples that it might be, but the devil would be in the details about the actual data.

But what we're talking about here is where you're not giving a therapeutic dose. Of the probes that are often proposed in the cocktail, I guess it's the Inge cocktail, you know, 100 mg of caffeine could be considered a therapeutic dose because that's about a cup of coffee, but, you know, 2 mgs of midazolam orally could produce some sedation, that may or may not--1 mg IV certainly would produce amnesia, which is what we as adults would get prior to surgery. But a 20 percent dose of losartan probably would have no impact on blood pressure.

So, what we're talking about here is the use of sub therapeutic doses which in my view, by definition, being sub therapeutic would not offer a prospect of direct benefit given that it is, in fact, meant to be a sub therapeutic dose, meaning a sub prospect of

direct benefit dose.

CHAIRMAN BOTKIN: Good.

DR. GLANTZ: I have thought of an FDA bureaucratic question. The guideline on exploratory dosing--on exploratory--or the Phase 0 studies, let's assume that they don't show anything, right, they don't show any activity. Is that the end? Does that mean that those--that a company or a scientist can't go on to the next phase?

DR. NELSON: I didn't hear the end of the--

DR. GLANTZ: Does that mean that the FDA would not permit this to go on to another--to, say, a Phase 1 study if it shows no activity in the Phase 0 studies?

DR. NELSON: First of all, let me preface that with a caveat by saying I don't reside in any of the review divisions, so treat what I say about that with a certain element of skepticism, but I don't think that would be a decision on the part of the FDA that that would

or wouldn't go forward, but the issue--the whole intent here is that in the absence of such an effect, I suspect a sponsor would not proceed because the intent of the exploratory IND studies is to try and see those effects and tease out products that would be more promising to move along the pipeline, but if--so, if there is no intended effect--I mean, clearly, one would have to discuss why one could proceed if then a Phase 1 came in with a Phase 0 that showed no effect, but, again, I don't have enough experience with all the detail to say--you know, I'm enough of a philosopher never to say something never will happen either.

DR. GLANTZ: Yeah, I'm just curious about whether or not giving someone 1/100th of a dose that's supposed to have an effect or in Europe, 1/1000th of a dose that's supposed to have an effect, if you find that--that it doesn't have an effect, then what does that--

DR. NELSON: I think the intent of the guidance is to make early exploratory IND

studies easier to do. It's primarily intended to reduce the bar for much of the preclinical toxicology studies that would be required to enter into Phase 1 testing, and if you're giving, say, 1/100th of a dose in--let's say in adults and doing some type of scanning study to see that, in fact, you can hit the receptor and you don't hit the receptor, I'm not sure it would take the FDA as opposed to the sponsor to decide not to proceed. I mean--but that's the intent of the guidance is to do that.

CHAIRMAN BOTKIN: Dr. Leeder?

DR. LEEDER: I took Dr. Zuppa's question to be a rhetorical question and it may not have been intended as such, and just sitting here thinking, in a hypothetical situation where a child has a disease state, let's say affecting liver function, you know, one might consider the use of a control group if the question is of a scientific nature and one wants to determine whether or not the disease process is associated with a change in

hepatic function that affects the clearance of medications.

If the intent of the study is to determine in that disease state if there are so-called deviations in normal that might ultimately lead to changes in dosing strategies, one would, I guess, argue as to whether or not a control group is really needed because the intent would be to improve the use of those medications in that disease state and having the information from a control group is not going to contribute to that.

So, it's--if you just limit the question to, does the disease state have an effect, one would argue that on a scientific basis you would want to have a control group, but in the bigger picture, it's not going to really add anything. Is that what you were--

DR. ZUPPA: Yes. Thank you.

CHAIRMAN BOTKIN: All right. We are--okay, one last question, then. Dr. Zuppa.

DR. ZUPPA: So, something I struggle

with, again, is this minor increase over minimal risk. So, for a lot of PK studies, an IRB will approve a protocol that includes placement of a peripheral intravenous catheter and sequential blood sampling for PK analysis as minimal risk, which is not part of everyday life. So, I struggle with what--I don't even know if I'm asking a question--but what additional risk is a 1/100th of a dose in comparison to a peripheral intravenous catheter placement and phlebotomies? And I just--I'm trying to tie in with the definition that was provided.

DR. NELSON: My suggestion is you hold that and when we show you the questions we'll get into that discussion.

CHAIRMAN BOTKIN: Yeah, I think that's going to be a significant element of our discussion around the table here in the near future.

So, we do need to take a break. Let's do that for ten minutes and, again, thanks to

Drs. Leeder and Nelson for their presentations this morning, and let's come back at 10:25.

[Recess.]

CHAIRMAN BOTKIN: Okay, we're going to try get started here, please.

[Pause.]

CHAIRMAN BOTKIN: All right. One of the things I may or should have mentioned at the beginning, and just a reminder for folks, there's not supposed to be any casual conversation at breaks or lunch or whatever about the issues of the day. Everything should be part of our official conversation here. So, that's a reminder.

We're going to turn next to the presentation of questions, but I do want to say that we have on our calendar or agenda 11:00 open public hearing, and that's at a firm and fast time for that discussion. So, whatever else we're doing before then, we'll halt at 11:00 and we'll open it up for public comments.

So, Michelle is going to present

questions for us that have been drafted, and these will be the focus of our conversation for the rest of the meeting.

DR. ROTH-CLINE: My greetings again to you all, and thank you for coming. The first question we're going to ask the committee to address, the administration of some drug and biological products may present more than a minor increase over minimal risk. Accordingly, a clinical investigation to study that drug must offer the enrolled child a sufficient prospect of direct benefit to justify that risk under 21 CFR 50.52. Under these circumstances, a study of drug metabolism may use, for example, a population pharmacokinetic approach as part of the trial designed to offer the prospect of direct benefit.

Our question to you: In some circumstances, could the use of a sub-therapeutic dose of this drug, of such a drug or biological product, reduce the risk to no more than a minor increase over minimal risk,

thereby allowing an exploratory IND study in children with the relevant disorder or condition under 21 CFR 50.53 or a minor increase over minimal risk? What, if any, are the circumstances under which this approach may be appropriate? What data would be necessary in order to make this risk assessment?

Question two: The administration of a single dose of some drug and biological products may present only a minor increase over minimal risk, based on adequate data in support of this assessment. Under these circumstances, a single dose pharmacokinetic and perhaps pharmacodynamic study can be performed in children with the relevant disorder or condition under 21 CFR 50.53.

Our questions to you: Could the use of a sub-therapeutic dose of such a drug or biological product reduce the risk to no more than minimal risk, thereby allowing an exploratory IND study in children without the relevant disorder or condition under 21 CFR

50.51 or minimal risk? What, if any, are the circumstances under which this approach may be appropriate? What data would be necessary in order to make this risk assessment?

Question three: There are other issues beyond the assessment of risk that may enter into the judgment about the ethical acceptability of a given clinical investigation, such as the scientific merit of the protocol, the social value of the research, the skill and experience of the investigators, or the potential for exploitation of economically-disadvantaged populations.

Please discuss how these and other relevant ethical considerations should factor into a decision to allow an exploratory IND trial to proceed. In your discussion, please clarify any differences in these considerations between a population of children with a disorder or condition and a population of normal, healthy children.

All right, and question four: There

is well-documented variability and deficiencies in the system of IRB review of clinical trials. In light of the discussion of the previous questions, how can we assure that children would be adequately protected if we allowed for the broader inclusion of children in exploratory IND trials?

And, Dr. Botkin, I will turn the meeting over to you to start the discussion.

CHAIRMAN BOTKIN: Thank you very much. We got our work cut out for us, and I want to first start this discussion by making sure we all are on the same page and understanding what these questions are. I think a second level of discussion might be whether there are additional questions that are not represented here that ought to be critical for our conversation, but let me start with just an invitation to our group to see whether these questions are clear, whether folks want additional clarification of the questions as posed.

[No response.]

CHAIRMAN BOTKIN: And I understand this is the first time folks have had a chance to look at these, so it'll take a little bit of time to absorb these.

All right, well, hearing none now is fine, and we may continue to invite questions about the questions themselves as the conversation develops here. So, let's go through these in order, and this is going to be a fairly freeform conversation about these particular questions, and, as we see, the questions build on themselves. One will be, perhaps, a little bit easier to answer than number two.

So, let me rephrase the question part of number one. In some circumstances, could the use of a sub-therapeutic dose of such a drug or biological product reduce the risk to no more than a minor increase over minimal risk, thereby allowing an exploratory IND study in children with the relevant disorder or

condition?

Loretta?

DR. KOPELMAN: Would these be drugs that are approved for use in children or are we talking about those that aren't approved for use in children? I mean, if they're not approved for use in children, then we don't have the evidence, right?

CHAIRMAN BOTKIN: Right.

DR. KOPELMAN: So, that's the difficulty here, right?

CHAIRMAN BOTKIN: Yes, I think the assumption is these would not be approved in children at this point and we're thinking about the so-called Phase 0 exploratory approach to these agents.

DR. KOPELMAN: So, you really can't answer this question?

DR. NELSON: Well, Jeff, actually, that is an answer to the question. In other words, by asking what are the circumstances under which you might be willing to consider a

drug that when administered at therapeutic doses to be greater than minimal risk, and, therefore, would require--under what circumstances would a sub-therapeutic dose of that same drug be considered only a minor increase over minimal risk? So, if what you're saying is one key issue is whether it's approved or not for use in pediatrics, meaning you've got already data about pre-clinical data, adult data, if appropriate, or data around safety and efficacy, then that's an answer to the question.

The intent there is to say what are the circumstances under which that approach may be appropriate, and if you're saying that one of those circumstances is whether it's actually approved for use, that is one answer, but then the question is: Would that be the only that would be the case?

So, the intent here is to hear, hopefully, a discussion of precisely those factors that would give one some confidence,

perhaps, in saying that this would be an appropriate assessment.

DR. RAKOWSKY: So, should the focus only be on the study product or can we all look at things like the necessity to a PET scan, for example, where we have a radiology risk or multiple blood-draws, which increases the risk? So, we'll have to push that into the equation here.

DR. NELSON: That was the intent of providing the component analysis aspect of the discussion is, yes, I think there would be significant differences about whether you just needed to get a urine sample for the study that Steve presented versus doing a PET scan with procedural sedation. I think that would be a significant difference.

DR. GLANTZ: So, before I think we can answer that question or before I can answer the question, I'd like to know what the risk is at all. So, if one-hundredth of the effective dose of dextromethorphan was given to a four-

week-old, what might happen? I feel like I need to be more concrete with the particular drug. What are the possibilities?

DR. LEEDER: In that case, yes, I would have to say probably nothing. In our consideration, we felt that sedation in those who weren't able to clear the making metabolized drugs efficiently might be most common a side effect that might be experienced.

DR. GLANTZ: Even at--

DR. LEEDER: Well, I mean, the bailout answer is we don't have any data to tell, but my gut reaction would be that one-one hundredth of the dose, we wouldn't anticipate too much.

DR. DASARATHY: Maybe it is just in my mind. I'm still not clear how do you define a minor risk over a minimal risk? I am still struggling with this because who decides what the risk is? Do the investigators decide this or do the parents decide this?

Then we come to an even more interesting question: How do we assess the

risk-taking ability of the parent? There are parents who push their kids to swim at the age of three years. Do I think it is right? I don't think it is right, but they may think it's right. So, how do you define or how do you accept that this is a minimal risk or this is a minor risk? And if the parents' values clash with the investigators' values, then where do we come to a consensus as to what the risk is? This is what has been in my mind since I read Michelle's paper. I'm still thinking how does one define minor risk or minimal risk?

I don't know who will answer this question. I don't even know how to answer this question.

CHAIRMAN BOTKIN: Well, I'll begin with a comment, just to say that, generally, it's the IRB who makes the determination about that. You may have an investigator who in the context of a particular protocol makes a pitch for a particular risk level and a particular

category of the approval for research, but, ultimately, it would be the IRB that would make that determination about the risk based on its considerations, perhaps, with expert input about the particular question and protocol at hand. With remarkable variability. The literature pretty clearly shows that on exactly these sorts of questions, you'll get a variety of different answers from different IRBs.

DR. DASARATHY: Then as a follow-up, I hold joint appointments in three institutions, and the IRBs are so variable. One IRB will say this is fine, the next IRB says this is unacceptable. So, am I ethically justified in doing this study in an institution which has given me the approval? And the same city, another IRB has said that is unacceptable. How do I deal with this? There's discord within IRBs.

So, and the other problem that we have faced in the past is that if one IRB has approved it and the other IRB has issues, and

if we tell them that it's already been approved at one IRB, then that raises a question whether the next IRB is going to say yes because somebody approved it.

Are they going to discuss the merits, or they'll say already it has been discussed, it's been approved, why should we go through this? Because we have had this happen, that it was disapproved in one IRB, then we went back and said it was approved in the other IRB. So, it was discussed again, and then said okay, we approve it now. So, this is very conflicting to me.

CHAIRMAN BOTKIN: Well, and of course, part of our conversation today is to help provide some conversation for the community about this sort of issue, and previous committees, SACHRP, IOM, have had some comments about minimal risk specifically, and there are certain traditions that have developed in the IRB community about what sorts of interventions are commonly considered minimal risk.

Just X-rays, simple films, those sorts of things so that there does become a certain community standards out there that are fairly common, but I think part of our conversation is to sort of help this conversation on this complex issue and move forward so that there is some guidance out there for IRBs about this exact question.

Norm, you have a comment?

DR. FOST: It's a question about point of order. Presumably, in answering these specific questions Michelle has outlined, we're supposed to be applying the principles that Skip outlined, and I have some disagreement with some of those principles as stated. So, I don't know when the appropriate point to discuss that is. I don't want to be out of order.

CHAIRMAN BOTKIN: Well, we're still on a pretty open phase here, so if you can be concise about that, I think we could welcome them right now.

DR. FOST: All right. There are three.

First, Skip referred to the "package deal," and the problems with the package deal and rejecting it, and I have a disagreement with that. I think he correctly stated the conventional wisdom on that and accurately quoted some discussions from the National Commission, but I think it's a wrong analysis, and, therefore, would change how we come out on these examples.

Everywhere else in life, we consider package deals all the time. I flew out here on a plane, if I paid my own way, the fare was substantially cheaper because the airline was stuffing some cargo in there, charging people for that, FedEx packages, and so on. It's not screened very well for bombs. So, it's increasing my risk. It has no benefit to me whatsoever, but it's part of the package deal. My fare is lower because of it, and I'm willing to accept all that.

Similarly, when I'm a patient in the hospital, medical students, interns, all of these learners come in, and I don't get any real direct benefit from that, but, overall, I think it's a good idea. So, it's part of the deal and I'm happy to be at a teaching hospital because I think--so everywhere in life in our ordinary experiences, package deals are appropriate.

Relevant to this, if I'm 1 of 50 million people with no health insurance and my child has a serious problem, and I can get him or her into a health care system and get really good evaluation of his asthma or his seizure disorder, whatever, in exchange for which I need to enter him into a study like this of very low risk by anybody's--it seems to me, that's a really compelling reason for me to enroll him or her in a study or if I were a fierce advocate for him, it's a good reason for him to be in a study like this if there's all these fringe benefits.

So, the whole idea of saying that it has to be a direct medical benefit seems to me not consistent with how we would ordinarily think of things. So, that's point number one. And that's in favor of a much looser or a much more permissive atmosphere in allowing these studies to go forward in situations in which the package might be beneficial to the child.

My two other comments go in the other direction, things that I think would be more inhibitory.

One is the regulatory requirement for more than a low risk, as Skip put it, to combine those two categories, which is helpful, I think, is that it must be a serious problem affecting the health of children or children with that condition. I'm not yet convinced even from Dr. Leeder's superb presentation that any of this is as serious, but not everything that we can advance knowledge about children is a serious problem.

It's all important work, I'm glad he's

doing this work, I'm glad others are doing it, it'll help us take better care of children in the future and so on, but not everything is a serious problem affecting children.

And when the National Commission came up with that distinction, and I was there for many of those discussions, what they had in mind were epidemics or diseases that were affecting tens of thousands of children and we can't learn anything about them unless we do some non-therapeutic studies that might be more than minimal risk, and that's why the Secretary should really weigh in.

Yes, this is a really big national problem. We've got this huge problem that we don't know what to do about. But not everything is in that category, and I think every scientist is very enthusiastic about his or her thing. So, doing all this sort of research that Dr. Leeder described is really important work and I don't want to trivialize it, but it's not like if I ask, for example,

will children really be worse off if we don't do any of this research, will there be a big problem? I mean, is that a serious problem affecting children?

I'm not convinced that, just to take a concrete example, one of the big breakthroughs here is the genetics of Coumadin. I happen to be on Coumadin. I've had to go off of it several times because I've had major surgery. So, I have to be recalibrated. They didn't check my gene because they sort of already knew how I respond to Coumadin, but knowing what the first, second, or third dose is, I don't see as how it would have changed my care at all.

You still have to check the INR on day two, three, and four, and then you space it out. I still don't quite get it. Maybe someone will explain it to me. What it does is strike me as a huge problem affecting adults or children that somehow solved Coumadin overdose and under-dose as a serious problem, but I don't see how knowing the genetics.

So, I'm not yet convinced, and Steve invited Dr. Leeder to say will this pharmacogenomics really substantially change the practice of medicine in 20 years? I haven't heard that case made yet. Maybe I just don't have a clear enough vision. So, that's my second point, is that the notion of this whole area of work that we're talking about today is really a serious problem affecting the health of children. I'm not quite there yet.

And the last point is just going back 40 years again, I'm still with Paul Ramsey, invading somebody's body without their consent for no benefit is battery. Len's the lawyer, he'll clarify this for me, but it's battery. And what is it that justifies this battery? We wouldn't do it to an adult. I wouldn't say to Jeff I can really learn a lot by just sticking one little needle in you. It's not going to hurt much, and it's got almost no risk, and I don't care whether you consent or not. You'd say that's outrageous. It's a battery, and

he'd take me to court.

So, I still don't get why we can do it to children, even if it does advance the interests of children. We could advance the interest of adults much more quickly and efficiently if I didn't have this pesky consent problem. So, therefore, consent assent thing becomes very critical, we don't take that seriously, and I, therefore, have a problem with the whole enterprise for reasons that were articulated 40 years ago.

CHAIRMAN BOTKIN: All right. Thanks, Norm.

I'll take Chair's prerogative here of inviting some feedback on these particular questions, probably one or two more, then three.

And, Skip, Norm was talking a bit about the package deal here, and I want to welcome some feedback from you specifically about that issue, and then from Dr. Leeder again about the value of this line of research

for children's welfare.

DR. NELSON: Well, a couple of quick comments.

First of all, I think, Norm, you're making a category mistake. You made very good argument for why going into a trial might be advantageous for someone from the standpoint of parental permission, consent, assent, but said nothing about the appropriate analysis of that risk/benefit on the part of whether the airlines should put unscreened packages in your plane. So, really, the question is not so much whether you should get in the plane, but whether or not the people that are screening it should do certain activities, and I think that's really what we're here to discuss.

To give an example of a problem with the package deal is there is a trial that I was aware of where an experimental monoclonal antibody was used, offered no benefit to the children, and the IRB decided that the protocol was beneficial because they received health

care that was, according to the policy of the country within which it was conducted, they should have received anyway. It was perfectly acceptable for the parents to want to go into that because they may not have been able to get the vaccine at a clinic, but the bottom line is they justified giving the experimental product, which, at that point, hadn't had much adult testing based on that direct benefit. That's just wrong. But the bottom line, that's just wrong.

Now, I'm not criticizing from the standpoint of the parents deciding to go into it. That may have been a very rational decision for them to do, but those are two different issues.

And then on the serious problem, I consider off-label pediatric use a serious problem, and when I mentioned the need for a public health goal, to me, concurrent licensure is a public health goal, and to whatever extent we can address issues in drug development that

lead to the point where we can have concurrent licensure, meaning pediatric and adult data coming out simultaneously, that, in my mind, is the default position. Any deviation from that needs to be justified.

So, these trials, the question of clinical impact, I think, is not unimportant, but I would also ask the question about the impact of these trials in the drug development process per se. Even if they don't have any impact subsequently on clinical management. So, that's the goal that I would say, in my mind, is a serious problem in pediatrics.

CHAIRMAN BOTKIN: Dr. Leeder, any quick comments?

DR. LEEDER: Sure. I'm busy trying to jot down a couple of points here.

One of the first responses would be that it's important for us not to get caught up in the height of pharmacogenomics and pharmacogenetics and personalized medicine. And it's important to realize that in a

population of a disease condition for which drug treatment might be considered, not everyone in that population is likely to benefit from pharmacogenomics. If we view it as a normal distribution; for example, clinical practice guidelines or dosage recommendations in the PDR, will probably be suitable for those that are under the hump of the distribution and maybe a couple of standard deviations.

The people who are most likely to benefit from the extra information that will allow their treatments to be tailored to their unique characteristics are those that are going to be in the tails, and the trick is being able to identify those individuals who in the tails, and that's where the value of genetic information will be. The rules are not necessarily going to be the same in children and adults.

The other thing is that the information that one can get from pharmacogenetics and pharmacogenomics may not

be of equal value to all disease conditions or drugs used to treat those diseases. And I think this is one of the things that have changed at our institution as to how we decide where to prioritize our efforts, and those are on disease-drug combinations that our clinical faculty think are important.

Obesity just happens to be one of the ones that we are starting to focus on, and I think it qualifies as an epidemic, and there is potential benefit to the individual and society if we can come up with adequate, and even better, really good interventions, that might impact the course of disease, as these children live for 40, 50, 60 more years. And I think that that means that we should be judicious in terms of where we invest our resources and not just spend an equal amount of resources for something that might be low frequency, low impact, when there is something that's high frequency, high impact available for those resources, as well.

I suspect that as things move forward, we are going to find that the situations that will benefit from genomic information are the same as those that have stimulated the FDA to take a look at drug-drug interactions. So, these would be priorities on medications that have a low therapeutic index, for example.

And, finally, going just back to the issue of warfarin, another thing that we need to take into consideration is that a lot of the studies that have been conducted looking at the value of warfarin, pharmacogenetics have been conducted in academic institutions' in tertiary care settings, and the value of something like genotyping may actually be in the small clinical practice in rural Kansas, where it takes a couple of weeks to get an INR done, and, unfortunately, we don't have any data from those types of practice settings to determine what the value might be to those who receive their health care inside of a tertiary care setting.

So, just some thoughts.

CHAIRMAN BOTKIN: Thank you.

I have Dr. O'Lonergan, Dr. Joffe, and Dr. Ross. We've got about two or three minutes before 11:00, and so, Terry, why don't you go ahead?

DR. O'LONERGAN: Okay. I think one of the problems with the package deal is that it can frequently be coercive. I think I can package a deal that you could not refuse if you were a parent. Having worked in marginalized populations, I think it increases the inclusion bias by including populations that are socioeconomically disadvantaged.

So, it thereby changes the burden and benefit distribution of the risk of research, and it's a way that we have found in the past to be unacceptable because it leverages social inequality, and thereby disadvantages people further. So, I think the package deal is a potentially coercive and disparate distribution of benefits.

CHAIRMAN BOTKIN: Dr. Joffe?

DR. JOFFE: I'd like to actually respond to a number of issues that have been raised both by Dr. Fost and by others.

On the topic of the package deal, I, some years ago, consulted on an adult study involving a Phase 2 trial with a very promising new agent for a kind of tumor that didn't respond to any known chemotherapy or anti-cancer agent, and so, people with this cancer were obviously very enthusiastic to get in this trial, and as a condition of being in this trial, people had to have accessible tumor that could be biopsied to do assays related to secondary endpoint.

So, it's not critical for the primary endpoints of the study. And the topic of the consult was a particular subject who said I really want access to this drug, I really don't want to undergo the liver biopsy that would be required for me as a condition of being in the protocol. And it's one thing to analyze that

from the adult perspective, where somebody can make a choice as to whether or not they're willing to accept that package.

The question that might come up, if a similar type of study were to be done in pediatrics, would it be acceptable to require a risky, invasive biopsy as a condition of having access to a promising new agent that parents and families and kids might understandably want access to. And I think that that would be a very challenging analysis to try to justify in pediatrics, when the risks of the biopsy were substantial, as they were in this case.

I also want to just make a comment about the concept of coercion and its application to the situation. It's one thing, I think, to say is it an undue inducement to hold out the promise of some promising new agent, but if you want to have the promise of that agent, you have to accept the risks of undergoing this procedure.

I think the concept of coercion may

not be appropriately applied in this situation. I understand coercion to be a threat to and pose some harm or withhold some benefit from somebody if they don't do what it is that you want them to do, and I don't see that as being the case here. Some benefit to which you have an established right. So, I think the concept of coercion, we have to be careful about using that word, and I think there are other concerns with the issues here, but I think that the concept of coercion is not one of them.

The second thing I want to address is the question of pharmacogenomics and tailored dosing, as raised by this, and my vision, today, we would say well, if the drug is approved in pediatrics and its dose is 10 mg for all children, you might say well, that's probably problematic because you probably don't want to give the same dose to a little kid as you would give to a big teenager.

And so, weight-based dosing or body surface area-based dosing is an advance over

just fixed dosing, and I think Dr. Leeder pointed that out in his talk.

However, imagine a vision of saying well, let's have an FDA-approved algorithm, whereby you go onto a Web site and you enter the age of the patient, the weight and height of the patient, the genotype of the relevant CYP alleles or other enzymes, and you're given a dose that's tailored to all those aspects of the patient, and it's a hypothesis that dosing in that way would be better than dosing just by weight that we do today.

But it seems to me a plausible hypothesis and particularly relevant, we've been talking about Coumadin, where you follow INR and Tacrolimus where you follow levels and other drugs where you follow levels, but for most drugs that are used in clinical practice and pediatrics, we don't actually follow levels, and so, you just take your best guess and either you get toxicity or you get efficacy or you get neither, and you're just sort of

taking your best guess.

And so, it may be for drugs like that, actually being able to tailor dosing according to genotype and age and the other things that we're putting on the table today would be advantageous for child health.

And, finally, on the concept of what's the serious problem, I don't know if there's a serious problem here, but it seems to me we should at least consider the possibility that failing to move toward some potential benefit is a real opportunity loss. It's not that there's an epidemic today, but there's a serious problem and sort of eminent threat to the health of children, but one can envision some opportunity and one has to make a decision, do we want to take the steps needed to sort of seize that opportunity or see whether there is a value to that opportunity or not.

And I see that the lost opportunity is something that's at least relevant to our

discussion today.

CHAIRMAN BOTKIN: Thank you. We're going to turn for a few minutes here to the public comment period. And I have a statement that I'll read, and then we'll welcome comment from the public.

This is the point in our meeting where we're open for public hearing, and there is a statement that I read as we begin this process.

Both the Food and Drug Administration and the public believe in a transparent process for information-gathering and decision-making. To ensure such transparency at the open public hearing session of the Pediatric Ethics Subcommittee meeting, FDA believes that it's important to understand the context of an individual's presentation.

For this reason, FDA encourages you, the open public hearing speaker, at the beginning of your written or oral statement to advise the committee of any financial relationship you may have with any firm or any

group, their products, and, if known, their direct competitors that's likely to be impacted by the topic you address in your presentation. For example, this financial information may include the payment of your travel, lodging, or other expenses in connection with your attendance at this meeting. Likewise, FDA encourages you at the beginning of your statement to advise the committee if you do not have any such financial relationship. If you choose not to address this issue of financial relationships at the beginning of your statement, it will not preclude you from speaking.

So, welcome any comment at this point at the microphone.

DR. WEINER: I hadn't quite expected to do this today, but given our conversation, I will. My name is Susan Weiner. I am the president and founder of the pediatric oncology advocacy group called the Children's Cause, and I've also been a participant in SACHRP and in

NHRPAC and various other forms in which children's research has been discussed.

I was a parent of a child with cancer who survived for more than 13 years. I was also a researcher, and so, one of the things that I've done through my organization and in my conversations is really to constantly strike the balance between the need for research for children in general, of course, but particularly for kids with cancer. And of course the need to protect against themselves.

One of the things that always concerns me about debates such as this is that we remind ourselves and not consider the notion of risk is a slippery slope, that we not expect or require kids who have a disorder or condition to assume a greater burden of research than others, that what we consider as the normal standard for minimal risk for these children has to be thought through quite carefully.

So, what might be a sub-therapeutic dose for a normal child might or might not be a

sub-therapeutic dose for a child with a disorder or condition. I think that that's important to understand and that the evidence has to be quite clear before one begins to engage children with a disorder or condition in research-only studies.

And, finally, I'd like to comment, once again, on the issue of bundling or packaging, which these days, is taking place in Phase 1 pediatric oncology clinical trials. The research community is split about it, and, to some extent, the parent community, as well. So that the notion of coercion actually does apply in the sense that if a parent is told you have a therapeutic option to enroll your child in a Phase 1 trial with a brand-new agent, but in order to expose your kid and assume the hope that it might benefit your child, you must subject this child to various PK tests for research purposes only.

The justification for the family to do so is for the benefit of other children. But

the emotional coercion of wanting to make sure that one has done everything possible for one's child therapeutically can't be denied. And so, I think that if PK studies in Phase 1 and elsewhere are to be a required feature of a protocol, they have to become a salient objective of the protocol itself.

So, thank you for the opportunity to speak today.

CHAIRMAN BOTKIN: Thank you very much.

All right, any other public comment at this time?

[No response.]

CHAIRMAN BOTKIN: All right, thank you very much. We'll close the public comment period.

CHAIRMAN BOTKIN: And back to our conversation then, and I think we have a couple of tracks here that are still going within our conversation. I believe Dr. Ross is next.

DR. ROSS: So, actually my comments

come interestingly after the public comments because I wanted to bring up one other issue with Skip's talk today, which was whether the prospect of direct benefit is purely based on structure and not on intent.

I think the language of direct benefit insinuates some degree of foreseeability and intent, because, otherwise, we'd be talking about benefit, which could be either indirect and things of that sort, and I think that becomes very important when trying to determine whether a Phase 1 trial, for example, should be understood by parents as a last therapeutic hope, and I think it raises the whole issue of the therapeutic misconception because the intent of the investigators is to understand the PK, and they're putting out this hope in order to enroll, and I'm very troubled by that.

So, I don't think that you can say that you can only look at whether--because, in some ways, determining whether there is a direct benefit only comes post facto, and you

don't know that beforehand, and so, the only thing you can know when approving the study is what the intent is. So, that's one point about why I agree with Norm, that before we get into the questions, we need to at least challenge the ethics overview that was given to us.

Skip also made the comment that in his mind that the ideal would be that the drugs would be approved at the same time for adults and children, and I think given that we talk about Phase 1, two, and three and enrolling dozens to maybe hundreds of people fails to acknowledge that when we do bring drugs into the community, when we do bring it to larger numbers, we learned a lot about a lot more risks than we started with.

And so, maybe we should be starting Phase 1 by the time we're in Phase 2 and Phase 3 in adults, but the idea of same time maybe a little overdramatic in the sense that, as a pediatrician and a general pediatrician, I'd rather expose the adults who can consent

themselves, rather the children, who, as Norm said, may be experiencing battery.

And I want to get to this issue of battery, particularly in the notion of this dextromorphan. So, while everyone was talking, I went on the Web to look up dextromorphan because I have to confess that, as a general pediatrician, even before it was taken off the market for the under two group, I don't think I ever prescribed it for a child under nine months or a year. And the idea of giving a drug to a two-week-old.

So, I looked through, and one of the things that I looked at was what are the other drugs that will affect dextromorphan metabolism, and one of things I all of a sudden got concerned about is if the mother is breastfeeding, and she may be on a multitude of drugs, particularly post-partum depression, she may be on Elavil, which they tell you don't take dextromorphan if you're on Elavil. Well, the infant technically isn't on Elavil, but the

infant is going to have levels of Elavil because it's going to go through the breast milk.

So, this notion of just giving a sub-therapeutic drug dose to a two-week-old, I have to tell you, I'm not sure it's ever just a minor risk. I don't care on what dose. We also don't know half the time what are the cause of SIDS, of Sudden Infant Death Syndrome, and giving drugs to two-week-olds and calling it minor risk, I'm finding very problematic.

So, I'll stop there.

CHAIRMAN BOTKIN: Skip, response?

DR. NELSON: Well, not to the last point because I think that's really a discussion point, but let me just make two points of clarification.

In my original slide deck, I had about four or five more slides talking about the analysis of Phase 1 trials and included a discussion of your articles, Lainie, that you've published and a more nuanced discussion

which would have to take place to sort that out.

My comment on intentionality was simply to point out that intentionality is not just a state of mind, but it's something that can be evaluated by others based on the actions which ones takes in the way that those actions are structured. That was surely the issue around intentionality, and nothing to do with the purpose of the protocol or it had nothing to do with therapeutic misconception, and to be able to sort out those issues would have required a much more extensive discussion. So, those slides were struck in the interest of timing. They were pertinent to the discussion of sub-therapeutic dosing, but maybe that was a mistake.

Second point on concurrent licensure, it's a misinterpretation of my comment to think that I was saying that Phase 1 and Phase 1 should be done at the same time. The challenge is do you end at the same time?

DR. ROSS: Right.

DR. NELSON: That's the challenge.

And in many circumstances, the answer is no.

In many circumstances, it might be that you would want post-marketing adult data before you would initiate certain pre-marketing data, but that's a deviation from the goal.

The question is: What would you set as the default goal, and then you make decisions whether you go earlier in the case of a life-threatening disease in pediatrics without any alternatives or whether you go later, in the case of something where you would want more adult data, safety data post-marketing before you begin pediatric trials. Decisions are made all the time, but the question is: What do you set as your a priori norm and then you deviate in one direction or the other based on the data. So, that's not my intent to say that those are inappropriate.

CHAIRMAN BOTKIN: Leonard, did you have a comment?

DR. GLANTZ: So, to try to talk about ethics for a moment, because we're talking about regulations, which, of course, is not ethics, that the question that Norm raises, I think, is when is it appropriate to deal with children this way? That's the battery notion, I think. What is the right way to treat children?

And Norm's point about sticking a needle in a kid is actually a dignity point rather than a risk point, I think. How do you go about treating children with dignity and what is it that we can do to children in order to benefit others? And so, we're asking the question of what is right, and that's what the hard thing is.

I mean, we could look at the language of the National Commission or we could look at the concept behind that language, and the concept behind that language is that there were things that aren't right to do to children unless you have like a really good

justification, right?

So, how do you justify using children in this way? And this is where they get to the point of that it has to be something of vital importance, right? They don't just say that it has to be important, but it has to be vitally important understanding thing, and that goes to the question of what is the benefit at the moment?

And so, we use the term clinical research for this, but I would suggest that it's actually not clinical research. I would suggest that this is basic research and that one is using kids. And I'm using the word "using" intentionally, in order to do basic research. And the children then become clearly a means to an end, right? That we need to do this with the children because they are the animal of last resort, if I could be as provocative as I possibly can be. A laboratory animal of last resort in this way. And the question is when is that okay, right?

So, we're looking for areas of justification to do to kids that we might otherwise not do to kids, like stick needles in them. We don't draft adults to be research subjects because we think having a lot of adults is a good idea. And the question is when can we draft in kids? And so, I think, ultimately, we're asking that question of what's right, and that's why it's like really hard. We could sort of make believe that risk is quantifiable or benefit is quantifiable, but we're asking for a justification to do that, which we otherwise wouldn't be allowed to do to children.

CHAIRMAN BOTKIN: Dr. Zuppa?

DR. ZUPPA: Kind of in response to much of the discussion, especially this comment. So, I'm a pediatric critical care doctor, and I can even just tell you, I mean, before there were conversations about there's not this epidemic of toxicity, there's not this epidemic of overdosing of children, but in

response to what Dr. Leeder said, are we appropriately providing pharmacologic treatment for children in need? Every time I'm on service in the ICU, it's a 50-bed ICU. There's an example of how we can do things better.

Just the last time I was on service, there was a three-year-old child with sickle cell disease, who suffered from an aneurism and intracranial bleed. And the neurosurgeons taking care of her work in both the adult setting and the pediatric setting, and she was having tremendous headaches, and they were like giving Nimodipine, calcium channel blocker will treat vasospasm. Went to go order it, and we were not allowed to give it.

Our pharmacy would not dispense it for a child of her age because there is no pediatric dosing guidance. So, she suffered through incredible headaches. We were limiting the amount of opiate we could give her because we didn't want to alter her mental status, and it was very frustrating. You could see the

frustration on the adult neurosurgeons' faces where they know this is a therapeutic intervention that can do right next door at the University of Pennsylvania, but we could not give here because we could not find that fine line between hypotension from the calcium channel block and the relief of vasospasm.

Another example is sildenafil to treat pulmonary hypertension. It's well-used in the adult setting. To use it at our institution, a few years ago, the director of our Pulmonary Hypertension Group had to get informed consent just to give it in a therapeutic setting, not into research, and now we have learned more from experience how to dose this as opposed to any type of PK studies or PG studies.

So, no, we're not faced with multiple episodes of toxicity or overdosing, but we are not providing the same level of care to children that are sick, children that are well, that we are providing in the adult setting, and every time I'm on service, I see an example of

this.

So, in response to question one, just to give you some settings where I think it may be appropriate is: Is this a setting where in this specific disease that there are therapeutic opportunities in the adult setting that we are withholding from these children because we don't have adequate information to provide rational dosing guidance? And would a microdose allow us to start to understand how to give this drug to a child in need?

CHAIRMAN BOTKIN: Thank you. I would also just pick up on a comment Dr. Leeder made a little earlier, too, which is we're certainly concerned about toxicity issues with kids for drugs that have not been adequately studied in the population, but the issue of consistently under-dosing certain segments of the population and kids who are not benefiting from those interventions, oncology being, obviously, a sort of extreme example of a subset of kids who might not benefit from chemotherapy because we

don't understand how their metabolism is metabolizing the chemotherapeutic agents.

So, under-dosing is as big a problem and perhaps sometimes bigger than the overdose issue.

Norm, I think you had a comment.

DR. FOST: Three very brief comments.

Just one last comment on the package deal, and then I'll get off of it. If it's morally problematic, then it's going on very widely, and it should be stopped. To be a patient at the clinical center at NIH with a rare disorder, you have to agree to be part of the protocol, which includes some elements of which have no direct benefit.

I agree with Steve that coercion is not the right word for that, but it's a difficult choice that parents and others have to make about whether to travel that distance and undergo various indignities and so on in exchange for the only chance you have to get a drug that's not yet approved for some rare

disorder. The same is true, more or less, for a lot of new IND studies elsewhere around the country, NIH-funded studies. So, it's a common part of clinical research is that the only way you can get into the trial is if you agree to be in a trial, and that includes some elements of which it may have little or no direct benefit. So, I think we do accept in various other settings.

Second, with regard to the example in the ICU of the child who might have benefited from, I agree completely that the lack of studies for this whole pharmacopeia that we haven't studied in children is a problem.

I agree with Skip that doing all of this just randomly and by the seat of our pants is not good, and there ought to be 100 X more dollars put into well-designed trials, and that, to me, is how your problem should be solved, that as children in your ICU and every other one who might benefit from that drug, there ought to be prospective, that is,

clinical trials that would offer the prospect of direct benefit, which might include pharmacokinetic and pharmacogenomic studies that would have no risk at all, just getting its samplings and so on from kids who already have central lines and so on.

So, I think there ought to be a logarithmic increase in those kinds of trials, and that's the way we ought to more systemically find out what the right dose and the safe and the effective dose to use for your kids. I don't know that it's necessary to do so-called non-therapeutic studies in those kids to get that answer. I think they can and should be enrolled in a clinical trial.

And then the last comment, and I'll maybe I'll save it for question two and three, because it has to do with non-therapeutic studies. The last point of order, Jeff, I want to go back to Lainie's comments and Skip's, that the devil's in the details. Can we be concrete? That is if we had specific examples

in front of us, I can imagine coming out very differently on question one for either side of it.

So, for example, for your question, for your calcium channel blocker question, should we do pharmacokinetic, pharmacogenomic studies in kids? Yes, but I think it can be done as part of a clinical trial. That's my answer to that one. If you ask me should we do a dextromethorphan study on a two-week old, a two-day-old to find out whether dextro, not as an indicator drug, but as a therapeutic drug, I don't care whether a two-week-old gets--I don't think it's worth it. I don't think that the problem of a two-week-old having a cold and a cough is worth it to give him or her a drug that may have some toxicity if it's not in the context of a therapeutic trial.

So, in that case, I would say no. So, I think it matters what the case is, how serious the disease is, what the plausible biologic risk is, and so on.

CHAIRMAN BOTKIN: Dr. Kopelman?

DR. KOPELMAN: I did. A couple of things.

First, the question of how to think about minor increase over minimal risk, I think there's confusion because there's so little agreement. I mean, there's certainly some, but if you think about do we agree about some things like minor increase over the speed limit, most people know exactly what that means. You can probably get away with 9 miles over the speed limit, but, what is the saying, 9 is fine, 10, you're mine, is what the police say.

So, we know we have a pretty good idea what you can get with speed limit, but when it comes to minor increase over minimal risk, we really don't have--studies have shown there's a lot of variability. There's variability between IRBs, among IRBs, and one thing that would be good to do would be to set up paradigms of what constitutes minor increase over minimal

risk.

The other thing I wanted to say was there really is a dilemma here, and, I mean, people are coming down in the abstract in very different ways about this dilemma because the values are so central and so important, the one value of advancing knowledge to help children, and the other, children in general, and the other is to protect individual children and their rights and their welfare, and the ranking is very difficult because the values are so important, and we are going to disagree about them, in many cases.

I'm a philosopher as I struggle to understand the Phase 0 trials. One thing that struck me is that you said the sponsor is going to make a decision about whether to go ahead with Phase 1, two, and three trials probably based on whether there's a response. So, my question is: Wouldn't there be some pressure to get the dose high enough to see whether you get a response, assuming you wouldn't get a

response at some low levels, but you would at some high levels. Wouldn't there be some pressure to get that dose higher, and wouldn't that be riskier without the Phase 1 studies?

CHAIRMAN BOTKIN: That's a specific question I think that Dr. Leeder might help us with. Would you want to give a brief to Dr. Kopelman on that?

DR. LEEDER: Well, I may need some clarification from the FDA, but my understanding is that the purpose of the Phase 0 outside of getting some initial pharmacokinetic parameters, you're looking at the distribution as the goal, and it's not so much to elicit a therapeutic response or a pharmacologic response or a therapeutic response of any sort.

DR. KOPELMAN: Did I misunderstand you when someone said that one of the advantages would be that the sponsor would not go ahead in all likelihood if there was no response?

DR. LEEDER: Well, I think there may

have been a discussion where the word "response" was used. To my mind, the response refers to some sort of change in physiological function in response to the administration of the small compound, but that is not--correct me if I'm wrong, that's not the original or the primary intent of a Phase 0 study.

DR. NELSON: Well, the word "response" here is ambiguous. So, there is responses that would be considered of physiologic interest whether you can show drug targeting in terms of having a marker that you could allow to hit the receptor, et cetera, and do scanning to see that, or, in the case of the studies that Steve presented, which I think are a concrete example, but more relevant to question two than question one, I would say, where you're looking at drug metabolism issues and doing phenotyping using sub-therapeutic doses, where you've given a dose that doesn't necessarily change blood pressure, but allows you to do a metabolic study looking at enzyme activity.

So, the response is the enzyme activity, that's a response, but blood pressure is also a response, and so, there's this gradient of response ranging from I can measure it in your body, but you don't feel it, versus you feel it. So, midazolam at 2 mg, I think we could debate whether you would feel it or not independent of the pharmacologist being able to measure it. So, that's where I think the word "response" is ambiguous.

DR. KOPELMAN: Well, whatever that response is, that would make the sponsor say okay, let's go ahead with Phase 1 or not go ahead with the Phase 1. I'm saying would that increment to give a higher dose so they do get a definite answer.

DR. NELSON: Well, the point is these phases are somewhat fuzzy. I mean, we use the term "Phase 0," but that's--you know, that's why the issue is exploratory IND. The intent, if you look at that, was to actually get even lower doses than were given in the examples of

the phenotyping example. I mean, one-one hundredth of a dose to find, according to preclinical toxicologies. So, that's even lower than some of these sub-therapeutic doses that would be used in some of these phenotyping studies.

So, I wouldn't get locked in to the Phase 0 or Phase 1 because it could be very fuzzy at the point which you transition, but Phase 1 is usually to where you are looking for some evidence, whether it's in maximum tolerated dose, whether it's 100 percent receptor affinity, which you would not be looking for in a Phase 0 or exploratory IND. So, one can't draw a dark line and say these are entirely separate, I think.

CHAIRMAN BOTKIN: Dr. Towbin?

DR. TOWBIN: Well, I've enjoyed the comments this morning quite a bit, and it seems to me coming back to the questions that at least the first question is framed in such a way that one risks quite a bit of

generalization. You can kind of say yes or no, and what worries me about the line of the discussion is that we might get to the point where we would say no, under no circumstances could such a thing be considered a minor increment over minimal risk, and I think that would presuppose that we close off any discussion of the circumstances or particular protocols or situations where that might be considered.

I think the devil is in the details, as Dr. Fost points out. I think we really do need to think about under what circumstances is the administration of an agent sub-therapeutic? It may not be therapeutic for all individuals even once you decide on a milligram per kilogram dose based on what their particular genotype alleles demonstrate and how they're going to metabolize that drug. And so, a great deal would need to be done to characterize those individuals. Those would be some of the details in the study that one would need to be

thinking about.

A second thing I wanted to respond to is that we're talking about children as if this is all one kind of uniform group, and what we think about with 2-week-olds and 1-month-olds is the same as what we would think about 10-year-olds and 12-year-olds, and I'm not sure that's appropriate for the considerations that we're having. I don't really regard drawing blood in an 11-year-old the same thing as drawing blood in a 2-week-old or a 1-month-old. My experience is that 1-month-olds find that quite a bit more aversive than 11-year-olds, although the 11-year-olds that I see regard it as highly aversive.

And so, I think that we need to understand those. Minimal risk may refer to the actual physical risk to the individual, but I also think that there are emotional consequences to being a participant in research, and, too often, those things are overlooked in the sort of risk-benefit

analysis.

The issue for these very young children is they are all, by definition, involuntary in their participation, and that, unfortunately or fortunately, we've allowed parents to make the decisions. Parents, as has been said a little earlier, can be very desperate for the care that their children receive and sometimes desperate to receive what would be standard of care when it's unavailable in their community and their locale. And sometimes that can cloud their judgment about what they're willing to expose their children to in the service of their getting what would be optimal care.

I guess the point for me is that we have to be careful in the way that we regard this question so that we think about the circumstances, and I would be uncomfortable about answering in such a way that I would get ahead of every possible configuration of study and research and close off the possibility of

learning more.

CHAIRMAN BOTKIN: Thank you.

Steven?

DR. JOFFE: I'm glad you made that point because it does, I think, lead us into how we might tackle this question. I was thinking about if one wanted to do a study of a pharmacokinetics of Tylenol and its metabolites and one wanted to give a single dose of 0.1 mg/kg where the typical dose would be around 15 mg/kg, it would be hard to imagine anybody saying that's more than a minor increment over minimal risk and probably we could even agree that that would be minimal risk. So, and then you can sort of imagine variations on that theme, right?

A drug that's approved in adults, but not in children. A drug that's approved neither in adults nor in children. A drug that's in Phase 2 testing, Phase 1 testing in adults and children. Where on the spectrum from .1 percent of the anticipated "therapeutic

dose" to the actual therapeutic dose. Where is the cutoff?

And so, we can begin to list the relevant factors without actually sort of setting the rules or establishing thresholds or anything like that. I don't think it's that hard to begin to come up with a continuum of relevant factors, and many of those have already been mentioned. Probably, we're trying to think of what the other ones are. Trying to then say what the thresholds are, I think, is going to be a very difficult exercise, particularly in the abstract when we're not faced with concrete cases.

CHAIRMAN BOTKIN: Dr. Dasarathy?

DR. DASARATHY: I guess I'm a little confused again over this question. What is the goal of this question? What is the endpoint when we're giving these microdoses? Is it just looking at the pharmacokinetics or is it to look at some kind of a response because we really don't expect a response in this. If the

goal is for pharmacokinetics, does the dose affect the pharmacokinetic studies that we do, and probably Dr. Leeder to answer because once you exceed a certain dose and maybe saturate on all the uptake pathways, transporters, or receptors, then does the response become different, does the kinetics become different? So, how much value is there to giving these microdoses?

DR. LEEDER: Well, I'm not an expert in microdoses. I've never done a microdosing study. For any of these, generally speaking for a drug metabolism study, you don't want to push the dose so far that you see satural kinetics because that may not be representative of what you're going to see with normal therapeutic dosing. So, you want to stay within the linear range, but I really don't consider myself enough of an expert to comment on microdosing studies or their benefits.

DR. DASARATHY: Maybe I can rephrase the question. So, would the pharmacokinetic

responses differ as the dose keeps changing, even within the therapeutic range? So, let's say you started at .1, then you study at .2, then you study at .5, and let's say the toxicity starts at 10. So, would the responses be different or would you get meaningful data at even the lowest dose?

DR. LEEDER: It depends on the drug, and a lot of those dose escalation studies are done in adults for a new compound before we would contemplate it in kids. Some medications that are used commonly that have this sort of dose-dependent or concentration-dependent metabolism, Dilantin is the one that comes to mind. But really it depends on the purpose of the study.

For the studies that I presented here, the issue was ontogeny, and so, we tried to come up a dose that we think has an acceptable risk benefit ratio, for example, and mostly what we're trying to do is minimize the risk. So, we go with the lowest dose that we can.

Things have changed considerably since we did those studies. Analytical capabilities are such now that one could probably look at patterns of metabolite formation at much lower doses. But the suggestion that has been made, and I forget by whom, that pharmacokinetics be considered maybe after the first dose of a clinical trial would really be helpful in this regard in terms of not looking at just a disappearance of the parent compound, but also the metabolites that are formed so that we can information on specific pathways at the same time.

If we were theoretically to design such a study, we would probably be taking a look at the adult data from increasing doses to see what the effect of the increasing dose is on the clearance, for example. Or, actually, Paroxetine, Paxil is another compound that has dose-dependent kinetics, as well. But that information we get from the studies that were originally conducted in adults.

DR. DASARATHY: Again, maybe I should redirect this question to Skip or to Michelle. What is the purpose of these studies if we are going to transpose data from adults and use that to do these studies? What is the goal of question number one? What is our endpoint? What are we actually looking for? What are we going to do with this information? So, why is this question there and what are we aiming for when we do such a study?

DR. NELSON: Let me answer the question this way, my bias, it's very difficult to do ethics without concrete cases. So, I would agree with those observations.

And the case that stimulated the purpose for this meeting, which is the case you have the consultation on and the discussion of the cytochrome P450 enzymes and the inclusion of healthy children, and that really fit with question two more clearly.

The reason question one was in there was as much for completeness around if you're

discussing something where most people, again, point of discussion, but most people will say the giving of a sub-therapeutic dose of something like whether it's losartan or something else could reasonably be considered by some observers and some IRBs to be a minor increase over minimum risk at a therapeutic dose for a single-dose PK study if you drop that down to where you get no effect, could that be minimal risk, and therefore, include healthy children? That's really question two in that example.

The reason question one was in there was to ask admittedly somewhat conceptually and without concrete examples may not be as productively as it could have been about whether that same question of the risk going from minor increase down to minimal, could it go from greater than minor increase down to minor increase under other circumstances, what would be those considerations?

My suggestion would be if it's hard to

wrap our heads around that question because there's no concrete example that can give you necessarily is that, I mean, I've heard a lot of discussions about different factors that are of interest, but, at some point, I think we should just kind of tackle the concrete examples and tackle question two because that's really the one that we do have a concrete example that people can get into a discussion of the specifics around the five compounds and the risks of those compounds and the kind of general considerations.

So, the desire in asking the question would be precisely to stimulate what are the considerations, which, in some sense, are a bit more difficult when you don't have a concrete example in mind, but I've heard useful comments on that discussion, nevertheless.

CHAIRMAN BOTKIN: Norm?

DR. FOST: I just want to get assent into this discussion because I don't think we talked about it adequately yet.

So, for the scenario one that Michelle outlines, I think risk is not a big issue because this is a child that's going to be getting this as part of a trial that has some benefit to him or her anyway. Secondly, even if that weren't the case, I think Steve's right, that there are drugs like Tylenol and so on that the chance of risk is so remote as to easily be categorized as a minor increase.

But, so it's not the risk of the drug that concerns me in category one or two, it's, frankly, the needle stick or finger stick or just that invasion. And if assent, the battery. So, if assent is going to be taken seriously, the point of it is to make sure that the child knows that if he or she doesn't want to do it, they don't have to do it because it's not for his or her benefit. They don't have to do it. And when a two-year-old screams when you stick him, he's conveying pretty clearly that he really doesn't want to do that.

And the reason that he doesn't want to

do it is the same reason a 23-year-old doesn't want to do it. It's because they just don't want to have a stick if they don't have to. Some do, some don't, but many don't, and the reason is not any careful weighing of benefits to society and altruism, all these things, it's just, all things considered, I'd rather not do it. And I think, overwhelmingly, two-year-olds, three-year-olds, four-year-olds, five-year-olds, six-year-olds, any age would rather not be stuck if they don't have to be.

So, if we're taking assent seriously, I don't know that it requires a lot of evaluation to decide whether or not the child really would want to do it. At older ages, you can ask them, and then you can start getting altruistic donations and stuff. So, if we take assent seriously, I don't know how you can justify even the single needle stick in the two-year-old, unless it's just some utilitarian analysis--well, it's in the interest of kids as a whole if we just stick some of them for the

benefit of others. But that gets back to my problem that would be true of adults, too. If we just get away with this pesky consent thing, we could advance the interests of the group as a whole. So, I don't think that fundamental core issue--and I'd love to hear Lainie talk about this because she's written a whole book about research ethics in children and so on and consent. But that, to me, is the fundamental, conceptual block about doing non-therapeutic studies in children, even ones where the drug is a minimal risk. But the stick is something that a child wouldn't want.

CHAIRMAN BOTKIN: Okay, I think Leonard, you had a comment.

DR. GLANTZ: Did you want to respond to that?

DR. ZUPPA: I did want to respond to that.

So, say you have a patient who has an indwelling catheter, a Broviac, an arterial line, they're postoperative, and there is not

the battery of a needle stick. But you are taking blood from the child. What is your opinion in--

DR. FOST: No problem.

DR. ZUPPA: So, it's the trauma and the pain of the needle stick?

DR. FOST: Yes.

DR. ZUPPA: Then but just to take my example further then, there is a risk of a central line associated bloodstream infections the more you access a line.

Does that become an element of battery to you?

DR. FOST: So trivial as to not bother me.

DR. ZUPPA: Okay. I just think there are so many gray areas.

DR. FOST: Yes.

DR. TOWBIN: Maybe in your sight, too. I mean, depending on how the rate of infection in Broviacs is handled in other places then it would be a consideration. And, again, I just

think that this is where one doesn't want to get too far ahead of excessive generalization.

DR. FOST: And just to be pragmatic, I'm guessing you're sampling that Broviac for clinical reasons, and Dr. Leeder just wants you to send a milliliter of blood. So, I don't know that even extra sampling is required.

DR. ZUPPA: It may.

DR. FOST: It may, yes. And so, again, it gets back to the details. If it's for a really important thing like looking at calcium channel blockers to help kids with serious problems and it's part of a clinical trial and you're adding--so, it depends on the importance of the study.

CHAIRMAN BOTKIN: Okay, and we have a couple of other comments, and in the near future here, I want to bring us back to the specific question and see where we are with that based on this discussion.

Leonard, I think you were next.

DR. GLANTZ: Thanks. So, the question

I would ask Skip, I guess, is are we to have a regulatory discussion or a discussion about the ethics? That we are dealing with statutes with regulatory language, and then it's a question of regulatory interpretation, in which case you could all leave the room, and the lawyer will take over because those are the people who do regulatory interpretation.

And I think one of the difficulties we're having is that we take this language seriously. So, the question of is there an interpretation of what constitutes a minor increment over minimal risk, and the answer is nobody knows, and that's why there's no regulatory definition of it because it can't be defined. It is an ethical expression of when is the risk low enough?

So, as Skip pointed out and Michelle points out in their article that Europeans don't use this concept; they use the concept of low risk. And then the question is: Is it low enough? And those are judgments. The question

is: Who makes the judgment of whether it's low enough? So, when you see clinicians and IRBs saying oh, a bone marrow biopsy, we do it all the time. It's like no big deal. And then you speak to people who've had bone marrow biopsies, they go oh, my God, a bone marrow biopsy, isn't that something?

So, there's almost a procedural question as opposed to a substantive one as to who's deciding is the question that was asked rather than whether or not you could quantitate it.

I think, Skip, you pointed out that you really can't quantitate it, that risk is something big. So, these are concepts, they're not biblical, they're not Talmudic, they're not Quranic. It's like we're trying to figure out justifications. One is the importance of the undertaking enough to justify the actual wrongdoing that Norm is suggesting that we're doing wrong and can be doing. So, we can get stuck in the language and we can say is it

justified?

CHAIRMAN BOTKIN: Skip?

DR. NELSON: What I can do is I think maybe when you get to question three, which the intent was to broaden the conversation around other factors besides risk assessment, I guess I'll hold my question to Norm about how one would apply the assent issue driving down below the age of two. I mean, I'd be curious if one ever waived assent based on lack of capacity even though there would be behavioral evidence of pain, but we can defer that question when we get past the risk assessment into the more broader discussion.

CHAIRMAN BOTKIN: All right. Let me see if I can force us into something like a decision on Question 1. And I do appreciate the challenge of having a lack of specificity on the other hand that gives us opportunity to be creative, and if this were a specific case, then our determination would perhaps only be relevant, then we have the opportunity now to

sort of dry out what factors might make this acceptable or not. So, let me go ahead and read the question again and then see if I can focus the discussion a little bit more.

In some circumstances, could the use of a sub-therapeutic dose of such a drug or biological product reduce the risk to no more than a minor increase over minimal risk, thereby allowing exploratory IND study in children with the relevant disorder or condition?

So, I think we want to, at least for the moment, eliminate other considerations like indwelling catheters, how you might either administer the drug or draw the blood to ascertain response and just think about the drug exposure itself at a sub-therapeutic level.

DR. ROSS: And this is a drug for whatever that child's disorder or condition is?

CHAIRMAN BOTKIN: Yes. Let's assume that the drug is one that's relevant to that

child's condition, but there's no prospect of direct benefit with the administration of the drug in this particular context. You're trying to answer a more basic question about physiology, pharmacokinetics, pharmacogenomics, et cetera.

So, the question, I think, we want to get feedback on: What are the factors, if any, that would make the exposure to that sub-therapeutic dose itself fit within our regulatory category of a minor increase over minimal risk? And you may wish to answer there's no such circumstance in which it would fit within that or you may wish to answer yes, I could see that it might in certain circumstances. Here are the specific circumstances that would make that acceptable to me.

DR. FOST: I'm just confused, and maybe I need Michelle to clarify. I thought question one is about a situation in which a child is part of a trial within the prospect of

direct benefit.

DR. NELSON: No. That's the usual paradigm, Norm, for a product that normally presents more than a minor increase over minimal risk. The question is: Outside of that usual paradigm, if we only gave a sub-therapeutic dose, single dose, would that be acceptable in 50.53? So, it's a question of deviating from the paradigm that you are identifying, which was the preamble to the question.

DR. FOST: So, we're talking about a situation let's say in which a child has asthma and he's not presently being part of a trial, but you want to find out if, say, LABA has some adverse effect on him, and you want to give it in a sub-therapeutic dose.

CHAIRMAN BOTKIN: No, I think the idea would not be looking for any necessary clinical response at all. You just want to get a very small dose to see how the--

DR. NELSON: Whatever product you

want, you have a relevant condition, a product's used for that condition, you're giving a sub-therapeutic dose for drug targeting, drug metabolism, or whatever other endpoint.

DR. FOST: But it's a drug that might be of some interest to that child because--

DR. NELSON: Well, the word "relevant" is meant to fit with the vital importance of knowledge pertaining to the child's disorder or condition, which is one of the criteria in 50.53. So, in that word "relevant" is buried all of that language.

CHAIRMAN BOTKIN: Dr. Towbin?

DR. TOWBIN: Just one here. When we're talking about conditions are we talking about illnesses and diseases, or are we also talking about, for example, the possibility that you would have two copies of an inefficient allele of 2D6?

CHAIRMAN BOTKIN: That's a great question. Probably less likely the latter,

unless that genetic status put you at some significant risk for future harm, in which case, some people might argue that that is the case, in fact, and so, I guess I need a little help in understanding the boundaries of what a condition are.

DR. TOWBIN: Some people might argue

CHAIRMAN BOTKIN: Well, let's think in terms of the more straightforward context in which you have a child with asthma or leukemia or something at this point because I think that's a challenging boundary issue.

DR. RAKOWSKY: Just to follow-up with what Skip just said, so relevant, looking at it from the IRB perspective, and there are ethics in some of the regulations, but I agree that we need to divide them out, but that's a big question that'll be asked: Is this microdose study actually part of a potential larger package? In other words, there is some vital information coming out from this. So, you're assuming right in that comment, relevant

disorder or condition that Part C of 53 is being satisfied.

DR. NELSON: Oh, that it meets the vital importance?

DR. RAKOWSKY: Yes.

DR. NELSON: Yes.

DR. RAKOWSKY: Okay.

CHAIRMAN BOTKIN: Yes, again, we had the luxury of making lots of assumptions in order to clarify exactly the question, and what we're trying to figure out at this point--

DR. NELSON: I really do want to focus it on the difference in the dosing and how that impacts on risk assessment. So, you can assume the other factors are appropriately considered.

CHAIRMAN BOTKIN: Good.

DR. ZUPPA: So, just for clarification, I would look at a Phase 0 microdosing as maybe to give some additional understanding of the disposition in a child that would guide. You could use that information to guide the dose selection for a

Phase 1 trial.

So, a drug that you may be weary to give even at a low dose, which may have a clinical effect, it would give you an idea of what their clearance is, what their absorption is, and then you could say hey, based on this, we can probably try this dose in the Phase 1 trial and it'll be safe, and maybe we'll do a dose escalation trial. We're not looking for adverse effects, we're not looking for clinical response; we're looking for some guidance as to how to move forward.

CHAIRMAN BOTKIN: Right, and not guidance for that particular child's enrollment in the Phase 1, but for children in general.

DR. ZUPPA: Or that child or--

CHAIRMAN BOTKIN: Okay.

DR. ZUPPA: Right, exactly.

DR. RAKOWSKY: And the assumption, also, is that in the pre-tox work and there's levels of having an exploratory IND, that there's enough work there to say that there is

very little expected toxicity at the microdose that you're giving. I mean, I think it's an important question.

DR. NELSON: Well, I feel like we're playing the game of Jeopardy here. You're giving the answer in a form of question.

DR. RAKOWSKY: Right. What is Socrates? Yes.

DR. NELSON: I mean, that's precisely one of the questions. When you go into a Phase 0 early exploratory IND, you do not have the same juvenile animal toxicology that you might have when you go into, say, Phase 2 and three in pediatrics. I mean, we do a phased approach, and so, you have to assume that there will be less information available, and the question is: Is that a problem? And so, by you asking that in the form of a question, it tells me that you think that might be a problem.

DR. RAKOWSKY: I think it's one thing if you have fairly predictable toxicity that at

some level you can say this is hitting the marker in animals that I think it's going to hit. If you're putting in, for example, a small molecule, say an exon-skipper, and you're not sure that's going to skip just on the gene of interest where it actually may skip in some other gene. I think you would be then hard-pressed to say okay, let's go forward because I think it's only going to impact on that one gene of interest.

So, I think that kind of has to go into the equation in terms of how do I look at the risk of this? Or a gene transfer, for example. If you think it's going to hit this part, and they can escape. You turn on an operon, with the retrovirus that wasn't predicted. In other words, that kind of increases your potential risk if you're not really exactly sure where this thing may be hitting based on animal data.

So, I think that's an important part to say how much comfort does this IRB in

knowing that the risks are not only minimized, but almost predictably minimized in a way that we can then move forward from microdose. I think the microdose itself is an issue. It's the potential non-expected safety risk of that microdose that you're looking at because the fact that you're giving a microdose that's for the pharmacological expected target, I think in and of itself is safe. What other targets aren't you hitting?

DR. NELSON: So, if I could just summarize your comment, the reason I put the quote up from the exploratory IND guidance about the fact that the purpose of it is to allow one to move forward in the absence of the same portfolio of animal preclinical toxicology, and then with the footnote about pediatrics is to render that issue problematic.

In other words, what I hear you saying is that, and I don't think we can drill in any more detail because we don't have products before us and how that might impact on the

testing, is that that assumption that you may have less preclinical testing that you would do in adult Phase 0 may be problematic if you consider the same kind of exploratory IND testing in pediatrics, depending on the nature of the product, the kind of toxicology you'd expect, et cetera, et cetera. That's what I hear being raised as an issue. I don't think we necessarily have to drill down more because you'd really have to get into the individual products and nature of the models and that sort of thing. Is that fair?

CHAIRMAN BOTKIN: Loretta?

DR. KOPELMAN: As I read question one, the question is: Couldn't the use of a sub-therapeutic dose? So, I read that to be is it possible? Can we imagine any circumstances whatsoever, and I guess if somebody was very, very sick, an adolescent, there were good adult studies. I can imagine circumstances where this might be a good idea, but if you're dealing with a child who's healthy, there are

no good adult studies, and the child is very young, then I would say no. So, it's very dependent, but I guess I could imagine circumstances under which this would be true.

Is this the question we're being asked? Yes? Yes?

DR. NELSON: Yes.

DR. KOPELMAN: I guess I can imagine.

DR. TOWBIN: That's kind of why I made my comment about how if you answer the first part of this no, then there's nothing to do going forward, and you've closed off any possibility for the future of the other elements of this. If you say yes, then the devil is in the details, as Norm so nicely put it.

CHAIRMAN BOTKIN: Steven?

DR. JOFFE: Up until about three minutes ago, I was thinking mostly about dose-dependent toxicities and their relevance here. And so, it struck me that, to some extent that you have some understanding of dose-dependent

toxicities, for example, from the adult setting, one could begin to make some judgments about the likelihood that there would be any significant risks to a child from some small fraction of that dose and be able to come to a decision about whether or not there was any significant or more than a minor increase over minimal risk of toxicity, and, therefore, envision some circumstances where one might go ahead.

Then it struck me what about the non-dose dependent toxicities that you sometimes see with drugs? I'm thinking particularly severe allergic reaction, severe rashes, those sorts of things. Not minor rashes, but some rashes can really be life-threatening, and really not dose-dependent.

And so, for a drug where it's approved and labeled for use in adults and it's been used in tens of thousands of people, sure, one can begin to make some judgments about that and that sort of thing, but for a novel agent, how

does one make those sorts of judgments where there hasn't yet been enough human experience to begin to quantify the risk of non-dose-dependent toxicities? And I'm not an expert in the sort of science and biology, and clinical aspects of this, but this strikes me as a real sort of hurdle to overcome in thinking about when one might do microdose studies or sub-therapeutic dose studies in children.

I would love to hear thoughts from anybody who might have some relevant clinical or scientific expertise here.

CHAIRMAN BOTKIN: Dr. Leeder, any response to that?

DR. LEEDER: I like the last part of that, any "relevant clinical...expertise" or experience, and I have none. As a non-clinician, I have no clinical expertise.

DR. TOWBIN: I think the only way to approach that is the line of argument that you're pursuing there would lead people to say why giving an agent at this phase is always

more than minimal risk. The risk of development something like Stevens-Johnson Syndrome or some hypersensitivity reaction that has never been seen before does exist, and there isn't a way to know that before you know it, and so, for some people, they would say if you ever give an experimental agent that hasn't been thoroughly tested in a variety of individuals beforehand to a child, you would run this risk.

So, I'm not saying that I necessarily agree with that, but I think that line of argument is why some IRBs have said any time you get an investigational agent to a child, that is something that is not already approved and where there are many, many adults who have gotten this drug, any time you do that, that's more than minimal risk just because of these concerns.

CHAIRMAN BOTKIN: And do we have any knowledge about whether the non-dose-dependent adverse events tend to be the same in kids as

they are in adults? Is this part of our conversation about having drugs that are pretty well characterized in the adult population?

DR. ZUPPA: It's not a response to your question. So, I don't know if anybody wants to answer your question. That's wasn't what I was going to do.

CHAIRMAN BOTKIN: [Off microphone.]

DR. ZUPPA: Okay. So, I'm going to go back to my Nifedipine example. In a setting where it's used frequently in the adult setting without high incidents of anaphylaxis or Stevens Johnson Syndrome or allergic response, do you think that in that setting it would be appropriate? I think so.

DR. TOWBIN: Right, no, I think that was exactly when we were talking about though Phase 0 kinds of studies where you don't have that kind of experience, I think that, again, I'm not stating my personal opinion, but having been in IRBs where such things have been discussed, that's the line of argument about

why giving an agent that doesn't have at least some very considerable experience in adults, giving such an agent to children would be seen always more than minimal risk. And that's all.

It isn't to say it should never be done or whatever, it just kicks it in to this other category.

CHAIRMAN BOTKIN: And I would say that I think that's a very accurate description of how IRBs have traditionally responded in this arena, although, I would say this opportunity we have today is a time to rethink that. Is that the right assessment that's relevant to this particular circumstance or not?

DR. RAKOWSKY: Just to follow-up on what Athena and Steve had mentioned earlier. If an IRB gets presented with the study where you're looking at a drug that's already well-characterized in adults, the toxicities both non-dosing and also unintentional toxicities are fairly well-recognized in adults or very sort of worked out in adults, unless the NIH

says do a pilot study just to see that NiImodipine even gets to the CNS before we fund a big migraine study in the ICU.

I think an IRB would probably feel a lot more comfortable because, in that situation, looking at a very microdose, granted that there is a vital importance, granted that the labs can be done in a way that doesn't increase the risk compared to a brand new agent coming along where you don't know what adjuvant may be in there, you don't know what this thing is being diluted in. You don't know what other unintentional toxicities are in there.

So, I don't think it's really the microdosing, per se. I think it's the comfort level that you have with the potential toxicities that kind of fit into here.

I mean, I think in your situation to say we'll do a 50-patient microdose to see if Imodipine even gets up there, I think a lot of IRBs would feel comfortable with that drug considering its use record in the past.

DR. ZUPPA: And on the flip side, I mean, so the setting in question one is it's the relevant medical condition. So, this is, in theory, a drug that can benefit that subpopulation with the relevant disease.

So, if, in fact, an anaphylactic response is dose-dependent, wouldn't it be better to know that with a microdose? So, in setting one, we want to use this drug in that population. And the Phase 0 is giving us some information on how to further those studies, a dose escalation trial on a Phase 1. I just wonder if the information gleaned from that microdose would--I don't know if I'm saying this right. It's not as if this is a drug that's not going to be used in that population.

So, I think that could give us additional information as to what the safety profile is to say. And I don't know too much about dose dependencies of anaphylaxis in the different settings, but I think so if you see an anaphylactic reaction with a microdose,

aren't you going to be darn happy that you only gave one-hundredth of the dose as opposed to the full dose?

CHAIRMAN BOTKIN: All right. We're past time for lunch here, and so, I want to see if I can push us one more step here, and it may be premature, but you can let me know if it is. So, let me lay out, again, the hypothetical that I think we're thinking about in this context.

So, we've got the prospect of giving a sub-therapeutic dose of a drug or biological product. We're not thinking about the context in which the administration itself would be burdensome or the assessment techniques as with blood draws, et cetera, would be burdensome. We're simply thinking about whether the sub-therapeutic dose itself would constitute no more than a minor increase over minimal risk. And let's assume that there is solid scientific value to the protocol in terms of understanding basic physiology, pharmacogenetics, et cetera.

Lainie?

DR. ROSS: I just need one more clarification because it's taken me all morning to realize that it's not just drugs, but we're also talking about biologics, which, even at the sub-therapeutic dose, remain in the body for weeks. We're talking about that, as well. Especially going back to Steve's comment of the non-dose-dependent side effects, this could be not pretty.

DR. NELSON: Well, so you're saying that the clearance of the product is a factor that would cause you to decide whether this is appropriate or not is basically what you're saying?

DR. ROSS: E pluribus unum, yes.

CHAIRMAN BOTKIN: So, I think we've heard of a number of factors that may be relevant to people's assessment of the risk in this context. How well has the drug been characterized in adults? What is the age of the child relevant to the population of

individuals for which the drug has been characterized to a certain extent? We have some understanding, let's assume, of the non-dose-dependent toxicities, as well as the dose-dependent-toxicities.

I guess the question I want to see if we're ripe for is: Are there circumstances? Is it conceivable in this context that you think this dosing would be no more than a minor increase over a minimal risk? And I guess I'm interested in a show of hands here whether folks could think of a conceivable circumstance where this would be the case?

[Hands raised.]

CHAIRMAN BOTKIN: Okay. And I think what we'll do probably after lunch is move on to question two, but we want to better articulate what these factors are and how they would play into this assessment.

DR. ELLENBERG: Do you want to call for anybody--

CHAIRMAN BOTKIN: Oh, yes. Well, we

certainly should do that. I didn't do a particular count, but let me see if there's specific--

DR. ELLENBERG: No count, but, I mean, is there anybody who didn't agree?

DR. NELSON: This is not a voting meeting, these are not voting questions. I think raising hands helps us understand the degree to which there's consensus around that possibility. But I wanted to say that so the audience who's use to having voting questions and formal votes doesn't realize why we're not doing that.

So, this is for guidance and for advice. So, having a straw vote is very helpful to kind of see informally, but it doesn't need to be a formal vote. These are not voting questions, including two, three, and four. None of that is voting questions. This is all discussion. So, I would consider that a straw vote and help reveal that. That's fine.

CHAIRMAN BOTKIN: Good. Thank you for

that clarification. I didn't see whether there were other people around the table who wanted to speak to a particular point there, but let's pick that up after lunch, and my thanks to everybody for outstanding conversation.

DR. NELSON: And so, for the committee, we'll be having lunch downstairs. I might say we will leave someone in the room so you don't have to worry about unplugging and taking your computers.

[Whereupon, the meeting was adjourned at 12:14 p.m. for a luncheon recess.]

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

[1:11 PM]

CHAIRMAN BOTKIN: All right. Let's go ahead and get started this afternoon. We've got a little less than two hours to address all of the issues that have been put before us. So, based on our pace so far, we have a challenge ahead of us.

I did want to invite Skip to give us a little bit more background on the product of this meeting. My understanding is there is some guidance in the works at the FDA and that this discussion may help assist in that guidance development.

Skip, could you speak to that for us?

DR. NELSON: Sure. One of our goals is to be able to develop guidance on the application of subpart D broadly. And we're sort of in the drafting phase, and I hesitate to say that because people say oh, good, we're going to have something quickly, but, as you

know, even if we finish guidance and even if that guidance within the FDA is felt to be suitable, then it goes to a process of clearance that often can be a couple of years.

So, I don't want to at this point give any hopes about when that might emerge, but in looking at that, I think when this protocol came up, I saw it as an opportunity to address an issue that I haven't seen addressed either in print, in publications, or in the conversation, and there's a lot that's been written about Phase 1, there's a lot that's been written about clinical trials, but I haven't seen much on exploratory IND trials in pediatrics.

And so, that's why I thought it would be a good opportunity to lay out some of these general ideas that we could then try to capture and incorporate into a general guidance. It won't be on exploratory INDs, but incorporate some of the insights into a discussion within part of that general subpart D guidance.

So, that's one of my goals, but I don't want people to have unreasonable expectations given the period of time it takes from my head to pen and then pen through many lawyers is a different proposition.

CHAIRMAN BOTKIN: All right, so not next week.

All right, I wanted to ask one more question about question one then before we move on to question two. And we've got some general feedback with some show of hands about conceivability in certain circumstances. I want to see if you we can potentially bracket that a little bit. And a factor that was stated by many in their comments was some familiarity with the agent in question. And, certainly, the SACHRP group that looked at subpart D issues made the recommendation that minor increase over minimal risk, while it's not defined, it should be articulated in the context in which there's some knowledge of what the risks are.

In other words, you can't call it a minor increase over minimal risk if you don't really have any data or familiarity with the agent in which to make that determination. So, I want to see how that plays out in that particular circumstance.

So, we talked again about a sub-therapeutic dose in this particular context, but let's imagine the circumstance in which we don't have human data about this particular agent. Are there circumstances in which a sort of first in-human trial in children would be considered a minor increase over minimal risk? Or is some information from the adult literature essential in making a determination of a minor increase over minimal risk?

Skip?

DR. JOFFE: I mean, I saw a lot of heads shaking when you asked: Are there some circumstances in which you might be able to consider this a minor increment without any human data? And I would certainly endorse

that. I would go further to say that particularly in light of the point I raised about non-dose-dependent toxicities, which is the thing that scares me the most about this area, that even some human data may not be enough because, as you know, to have any beginning of an inkling about the likelihood of non-dose-dependent toxicity, you need experiences of at least hundreds if not thousands of human exposures, and so, I think even to contemplate a drug that had been in 50 or 100 adults through phase 1 testing, I'd be very anxious about considering that in a Phase 0 or exploratory IND kind of study in pediatrics because of the possibility of a Stevens-Johnson type reaction or a severe hypersensitivity reaction.

Again, even if one had some sense of the dose-dependent toxicities where you don't actually need quite as many people to begin to at least learn something about the more common ones.

CHAIRMAN BOTKIN: Norm?

DR. FOST: Just two examples to make this concrete, this is not remote and theoretical. Lainie mentioned during the break--I know we're not supposed to talk during the break, but--

DR. ROSS: [Off microphone.]

DR. FOST: It's all Lainie's fault. The pituitary-derived growth hormone had an uncommon complication, but lethal, and you wouldn't want to be--I mean, it was bad enough that that drug has been given to so many children who don't need it anyway and who get no benefit from it, but to do it for not even a theoretically beneficial reason would have been a major tragedy. That's one.

And another one is the zinc porphyrin study I was starting to talk about before. This is a drug, amazing, that could end neonatal hyperbilirubinemia. That is, it interferes with the conversion of bilirubin to hemoglobin, and it's incredibly effective, and

I think it's a single dose, but the problem is in radio-labeled studies, it appears in the brain a year later. So, there's zinc flowing around in animals at a year of age in their brain, and, yes, who knows what a little zinc in the corpus callosum does.

So, those are just two examples of single dose, non-dose-dependent major toxicities.

DR. TOWBIN: Just for me, the issues of capacity and assent that are so critical here just really can't be overridden under the circumstance that you draw out. One would need to have plenty of adult data to be able to talk about with parents to really assure that there was some background, and I, for one, would feel very uneasy about doing first--in-human studies in children without any adult data at all.

CHAIRMAN BOTKIN: Dr. Leeder?

DR. LEEDER: Yes, I think the importance of adult data is critical, and I can think of one situation where a

hypersensitivity-like reaction, at least its frequency in kids, would not have been appreciated from just solely adult studies, and that would be from lamotrigine has a higher frequency of cutaneous adverse drug reactions in kids likely has a developmental component with the glucuronyl transferase pathway, but has not been really looked at in depth, but certainly a higher frequency in kids, hence, the start low, go slow recommendations.

CHAIRMAN BOTKIN: All right. So, it looks like it goes around generally that good-quality animal data is essential, but not sufficient in this circumstance, and we would want some experience with the agent in adults in order to characterize what the risk level was with children.

All right, let's move on then to question two. I'm going to go ahead and read it for us. The administration of a single dose of some drug and biological products may present only a minor increase over minimal risk

based on adequate data in support of this assessment. Under these circumstances, a single dose pharmacokinetic, and perhaps pharmacodynamics study, can be performed in children with the relevant disorder or condition.

Okay, so here's the question: Could the use of a such sub-therapeutic dose of such a drug or biological product reduce the risk to no more than minimal risk, thereby allowing an exploratory IND study in children without the relevant disorder or condition?

So, I believe what we're doing is taking the same fact set and then--not entirely the same fact set, but basically asking the same question about minimal risk that we did over minor increase over minimal risk.

Dr. Kopelman?

DR. KOPELMAN: There are some conceptual problems with this question that I think need to be explored first. Minor increase over minimal risk for children which

is permissible for children with conditions is generally understood as a relative standard. Minor increase over minimal risk to their condition.

Now, that often allows more than for healthy children, but it needn't. I mean, if a child has an immune disorder, they might be in great danger being exposed to other children in a playground, which would be certainly permitted for healthy, normal children. So that that category is linked to the child's condition what would be a minor increase over minimal risk for that child whereas many of us read "minimal risk" as keyed to normal, healthy children.

So, again, I don't know how to answer that because it isn't clear that it would step down. I guess that's what I would say.

CHAIRMAN BOTKIN: Dr. Towbin?

DR. TOWBIN: Well, I think this takes us into a different arena altogether because if we make this determination that the

administration of this sub-therapeutic dose is minimal risk, then as the case was presented, the hypothetical case, this does open the door to doing this with healthy volunteer children. Minimal risk is not something that changes with the group. In other words, something isn't minimal risk for children with a condition and more than minimal risk for healthy volunteers. If it's minimal risk, it's minimal risk.

We usually don't tie the risk to the condition, and so, I think the question that's being posed there--this is more a comment than a question. I think what's being posed here is whether offering sub-therapeutic doses of agents is something that would be acceptable for healthy volunteer children.

CHAIRMAN BOTKIN: Yes, and I think that's the specific question. I think also with this conversation, maybe we can help folks as we had previously, to eliminate concerns initially over sort of root of dosage, so that we're not talking about the risk of indwelling

lines or the risk of multiple blood draws, perhaps, and we may want to get back to the specific protocol that was part of our packet, but at least at this point, I think we want to think about the risk of a sub-therapeutic, perhaps microdose in some circumstances and whether we would ever consider that to be minimal risk.

DR. TOWBIN: But one follow-up, if I can, to my comment is that the phraseology here is it can be performed in children with the relevant disorder or condition, and I think what we are actually talking about it is can also be performed in children without any disorder or condition.

CHAIRMAN BOTKIN: Not seeing folks leap forward with additional thoughts about this--Leonard?

DR. GLANTZ: I'm not sure why this is a different consideration than the previous one. I'm not sure why this is a different consideration than the previous discussion in

which you have to know something about the risk. I mean, you can't make a risk decision, you pointed out, Jeff, without knowing something about the risk. If you can't make a minimal risk decision, particularly non-dose-related effects. So, I don't see why this isn't essentially the same question, unless I'm missing something.

CHAIRMAN BOTKIN: I'm seeing a number of hands, and I would go back to Dr. Towbin's earlier observation, which is the fact that I think many IRBs consider the administration of any drug to be never minimal risk. I don't know that I've seen literature on that particular determination, but I think it's common experience. So, I think we're raising that exact question here: Are there circumstances in which, perhaps, dose decreases might fit you under a minimal risk category?

Dr. Zuppa?

DR. ZUPPA: I think the difference between question one and question two is the

risk benefit ratio. In question one, the drug was relevant to the disease of that pediatric subpopulation. So, it would benefit children with that disease and may actually benefit that child at a future date. So, I agree that the risk itself has not changed, but in question two, there is no potential benefit to that child in the future. So, I think the risk benefit ratio changes in the two settings.

DR. RAKOWSKY: Actually, I think between question one and question two, question one was the risk level three. There is sort of less certainty that there is absolutely no risk at all, but you think it's still just a minor increase over the minimal risk. To do it in a healthy subject, you'd have to a risk level one study, where I think you almost have to have a real certainty that there is no either unintentional risk of dose-dependent risk or dose-independent risk involved and sort of being an oxymoron to do a risk level one, I think there's no risk study as an exploratory

IND because part of the reason for doing an exploratory IND is kind of figuring out how the drug works.

So, I just don't see how the two mesh together in all honestly.

DR. TOWBIN: So, I wanted to follow-up on Mr. Glantz's nice point here. I think that actually Dr. Zuppa's comment and his comment dovetail very nicely with how I think about this. If something is more than minimal risk, it still is in this low risk category, but in order to pursue that for healthy volunteer children, one is still stuck with it's not minimal risk, and there has to be, I think, a more serious discussion about what the risks to their healthy volunteers would be.

In this second question, it's relegated to minimal risk, where there is clearly no benefit to the child. In the first question, we were really thinking about someone with a condition, where giving this agent could be informative for other individuals who also

have that condition, and those elements of altruism that we talked about could still be applicable, and whether generalizable knowledge to other people with that condition would apply.

Where you're giving an agent to healthy volunteer children, the concern is that they really don't have a particular problem, and so, they accept the risk without any benefit whatsoever to them or the group of individuals who are also healthy volunteers because they would not be likely to be getting these agents.

CHAIRMAN BOTKIN: Skip, I think you were next. Skip?

DR. NELSON: Well, I was just going to suggest that we can bring general observations down to sort of a level of specificity that would be helpful as we actually tackle in answering questions about risk.

For example, the hypothetical protocol that was distributed as part of your background

package. And so, your specifically asking if you wanted to concretize this question, is giving an oral dose of 100 mg of caffeine, 20 mg of omeprazole, 25 mg of losartan, and 2 mg of midazolam minimal risk?

I mean, so that would be helpful to at least start as a base and then instead of going to the general to the specific, let's go from the specific to the general. I think you've got the question exactly right. I don't think it's a conceptual issue. I think you expressed the concept perfectly. The question is: Do these fit?

CHAIRMAN BOTKIN: Good. We had a couple commentators, and we want to pick up on the specifics of this trial, and I will welcome here in a minute a little bit more comment about the specific doses being used in this trial to give us some more background about how sub-therapeutic is sub-therapeutic, but I think Len had a comment, and Lainie, as well.

DR. GLANTZ: I just wanted to respond

to Dr. Towbin's point that, to me, it doesn't matter whether or not the child is in a group that may benefit if the child's not going to benefit.

So, the fact that all children may benefit as opposed to just this group doesn't move me either. And it doesn't tell you what the risk is. It may tell you whether or not there's justification for doing the research regardless of what the risk is. But it doesn't change that the risk analysis--the point I was actually trying to make is that, the point that was made is that you can't decide on a risk level until you know what the risk is in children.

So, it seemed to me if we said that you need adult data before you could even begin to think about the risk if you would need that for number two, also.

CHAIRMAN BOTKIN: Lainie?

DR. ROSS: So, actually, I agree with what Len just said in contrast to what Dr.

Zuppa had said. You can't talk about in question one that it was a benefit to the child because it wasn't a direct benefit to the child. It may be a benefit to the group in which he or she has a common trait, disorder, or condition. It may be that in the future, he or she will benefit from that drug herself, but that's actually true of healthy kids, too. Healthy kids become adults, and we eat too much, we don't sleep enough, we live a stressful life. We're all going to end up with hypertension and all the other health problems that adults have.

So, I mean, so to use the argument, again, the regulations are specific. It's about a direct benefit, and there is no benefit to the subject. There is no direct benefit in either question one or question two. So, let's not delude ourselves with the therapeutic misconception. These are non-therapeutic, not meant to be direct benefit studies. We can go from there.

DR. GLANTZ: To the subject.

DR. ROSS: To the subject

CHAIRMAN BOTKIN: Norm?

DR. FOST: I agree with both of those comments, and I just want to put it back in the context of the conceptual points I made earlier.

So, we have this battery occurring, but we decided to sort of wink at it because of some utilitarian calculation, that it'll be good for children in general or at least children with that condition. But just we want to draw a perimeter around that to make sure nothing really bad happens, and we have three perimeter defenses, one of which is that a responsible parent will protect the child.

That hasn't worked perfectly because parents have acquiesced to things that are way more than minimal risk by anybody's notion. We have IRBs as another perimeter. That hasn't worked. They've tread way beyond what was intended. You have parents. That hasn't

worked. You have this minimal risk. That hasn't worked. IRBs have approved intestinal biopsies and all sorts of other things. And then, last, you have assent, and that's not being taken seriously.

So, in my view, none of the four perimeter defenses we have to stop bad things from happening have worked. I mean, it's not really common that we have these transgressions, but they're well-known. So, in both of these cases, one and two, therefore, we're invading this kid's body for no plausible benefit to him or her, and you don't have these protective mechanisms, and I think they're both problematic.

Does that mean you could never do it? No. I've sketched that earlier. I think there are circumstances in which it is okay.

Finally, to answer Skip's very appropriate request for a concrete example, mainly the Burckart consultation, I thought Dr. Burckart's analysis was correct, and he came to

the conclusion that it really wasn't necessary to these studies, that you could get enough information from adults and from adolescent populations that you didn't have to do anything that was in the context of direct benefit trials. So, to take that example, I think you could get the information you need without violating any of these principles.

CHAIRMAN BOTKIN: Dr. Zuppa

DR. ZUPPA: No, I'm okay.

CHAIRMAN BOTKIN: No, you're okay?

Steve Leeder?

DR. LEEDER: Well, let me suggest that times are changing a little it. There may be some individual benefit to individuals participating in phenotyping, genotyping study.

For example, we have had requests from parents for their child's genotype results to be returned to them. And part of the reason for that is that in the consent form, it says that cytochrome P4502D6 or P453A4 is a pathway involved in the breakdown of medications used

to treat, and then it lists a bunch of diseases. And they'll say oh, well, my child has ADHD or something else, and for them, they want to know that information. And so, now we are dealing with trying to identify a structure in which not only can that information be returned to the family, but also to the primary care pediatrician in whose care that child is under.

We have also had situations, and I can think of one emergency room physician, on back to back days, had a child come into the ED with a genotyping report from the Mayo Clinic with their CYP2D6 results, wanting to know what medications they could take safely, and another one, another family who had been referred to our emergency department for cytochrome P450-2D6 genotyping by a child psychiatrist in the rural part of the state.

Parents are very much familiar with the things that are going on, especially if it's related to a condition that their child

has. In some cases, they are better informed than many of us. And I could see a point in the future where the issues that we're dealing with is going to be how to return the results of these studies to the parents and pediatricians in a responsible manner.

In our particular case, we happen to have an individualized pediatric therapeutics clinic, and what we have proposed to our IRB is that the results will be returned to the family in the context of a visit to this clinic, and it'll be delivered by a clinical pharmacology trained general pediatrician or licensed health care professional. But it's coming, and it may be of value to some parents to have that information. What one does with it is a completely different matter.

DR. JOFFE: I'm looking at this Burckart consultation and thinking about the four drugs and the doses that are in there. Losartan is the one I'm not really familiar with the sort of typical dosing in clinical

practice, but so the fact that four doses are aggregated in a single cocktail complicates things, and there's probably more than the risk of any one of those drugs by itself.

If you were to disaggregate it and give it as four separate drugs on four separate days, then that would reduce the risk of each component of it. One hundred milligrams of caffeine, I had no idea how much caffeine was in a cup of coffee or a bottle of Coke. I just looked that up. It's about 24 ounces of Coke would give you the same amount of caffeine as this protocol.

So, it seems that 24 ounces of Coke is sort of daily life, and I'd be fairly comfortable saying that that exposure by itself in a kid that had no particular risk factors for caffeine toxicity would be minimal risk. Two milligrams of midazolam given orally strikes me as a potentially pharmacologically active dose and might increase the risk of somebody falling on their way or an older kid

who was going to then drive home, having increased risk in the car.

So, I'd be sort of uncomfortable about that. But if it were half a milligram or 0.2 mgs or something like that, we could probably come up with a dose where I might be comfortable saying minimal risk, again, assuming that anybody who is at increased risk because of some individual factor was screened out. Omeprazole, we have similar conversations.

So, I think, in principle, it's not hard to work through this and identify some dose, and these are very well-known, well-understood agents, where we could say this is minimal risk for some particular population of kids. I realize that this is not the same as an exploratory IND when we're talking about some novel agent.

CHAIRMAN BOTKIN: Thank you. I do want to look more specifically at exactly these sorts of issues, and I think the concern that

Norm raises, obviously, is a legitimate one in its particular context. Is this the type of science that is fully justified in this particular context?

I want to bracket that question at the moment and assume that this will provide valuable information to investigators about drug metabolism. And I want to look specifically at this cocktail. So, we've got 100 mg of caffeine, 20 mg of omeprazole, 25 of losartan, and 2 mg of midazolam.

So, to what extent are these sub-therapeutic doses, and I'm looking at Dr. Leeder, unless others have expertise. Dr. Leeder, I wonder if you can comment briefly on the sort of doses we're looking at at this cocktail and the protocol that was distributed for us. I think the hypothetical that we're trying to deal with is sub-therapeutic, and so, questions have been raised about whether, in fact, these sorts of doses are sub-therapeutic. So, a quick comment on that, and I think then

we want to take the hypothetical where the doses might be substantially less and to clearly make them sub-therapeutic and see how that changes our conversation.

DR. LEEDER: Well, I'm a little bit less comfortable with a fixed 100 mg dose of caffeine. To me, that seems like a--now, this is just my personal opinion. I'm not calling out any literature to support it. To me, number one, a fixed dose, I don't think if you're metric to measure a drug-metabolizing enzyme is a single point. The higher the dose, the higher the peak concentration you're going to get if that's what you're measuring.

And so, to give fixed doses of these to children of varying bodyweight is, in essence, a difference in dose, and you can expect variability in the concentration that's achieved by virtue of the fact that you've given different doses.

So, the 100 mg dose is high. I have really no sense of losartan. What I would like

to see is where the concentration after the recommended dose, what the concentration profile looks like relative to an analogous dose in adults before making a decision as to whether it's too high or acceptable because the issue with midazolam is that of sedation, and I don't think that one would want to make sure that the child, the study subject, or the patient, if this is being done on an outpatient basis, is not suffering from any untoward effects of the components of the cocktail before they leave the unit. And I don't know how you would determine a point at which there is not excessive sedation really.

We would not at our place release anybody from one of these studies to go home by themselves. It would always be in the care of the parent. But my just kneejerk reactions to the doses is that of caffeine being high. Not being able to evaluate the losartan, but just in general, having an aversion to fixed doses in a pediatric protocol of any type.

CHAIRMAN BOTKIN: So, I'd be
interested
in--

DR. LEEDER: Phenotype. Sorry.

CHAIRMAN BOTKIN: --inviting comment
from anybody, again, about this particular
cocktail at those doses and normal controls age
12 to 18 I'll say for our context. Less than
18.

Do we wish to comment on whether this
constitutes minimal risk or no more than
minimal risk?

Dr. Zuppa?

DR. ZUPPA: There are children, too,
who have a paradoxical reaction to
benzodiazepines and cannot feel good, don't
feel good after they get them. So, I don't
know if it's necessarily--I think 2 mgs is a
generous dose, and there is risk of that
associated with that dose administration.

DR. TOWBIN: And actually we do have
some data about those paradoxical reactions,

which are much more common in children than they are in adults. About 15 percent of children will have paradoxical reactions to benzodiazepines, if I recall correctly.

DR. ROSS: I've had at least two adolescents develop SVT after that much caffeine, probably less.

CHAIRMAN BOTKIN: So, we're hearing reports of adverse reactions and doses that are being described here, as well as the possibility in a carefully-designed protocol of a monitoring period after doses of this sort.

DR. TOWBIN: I think the other thing to be said is, again, we're grouping all children together. How many parents would allow their 1-month-old to have 24 ounces of Coca-Cola?

DR. JOFFE: Just to note this was a protocol for 12 to 21.

DR. TOWBIN: Sorry, although the question doesn't speak to it that way, and, again, I think the issue of what constitutes

minimal risk would have to be considered under those circumstances, as well.

CHAIRMAN BOTKIN: Yes, so are there circumstances in which this particular cocktail in this age range would constitute in people's minds no more than minimal risk?

DR. DASARATHY: We have also had these paradoxical reactions with midazolam. The question here is you're mixing caffeine, which is a stimulant, with midazolam that is considered to be a sedative, which can potentially become a stimulant. So, these are unanticipated interactions.

We are not even considering--and that brings me to Steve's suggestion, that in sort of making these cocktails, it's probably a better idea to use them individually so that even if there are issues, we will deal with them one at a time, not find out unintended interactions for which we have no control or no knowledge of.

CHAIRMAN BOTKIN: Yes, Skip?

DR. NELSON: I think these are useful comments, and what I'm hearing is behind this is, sort of I might articulate a general principle of the lack of physiological effect. I mean, there might be some doubts about the caffeine in the midazolam, as to whether that's true or not that the losartan is about 50 percent of the starting adult dose. So, but that would be a question.

What's interesting to me here is the discussion of the single drug versus multiple drug, which I think is very relevant. Actually cuts against the desire to minimize risks of the other components of the procedure, which is precisely the blood-drawing, because if you then end up doing this four times for four drugs, if an individual would, in fact, assent to do that as a teenager, you then have four peripheral lines for blood-draws for each one.

So, I guess I want to problematize the balancing of the judgment between the risk of mixing these together, which I agree with,

against the let's call it burden since it's not a risk, it's a known burden of having a line in four times if you're going to do it say once a week for four weeks instead of just once one day.

DR. DASARATHY: I guess that brings us to the problem which, in our judgment, is a bigger risk. Is the risk of multiple pokes and the discomfort with it more than the potential risks of unknown or unintended drug interactions? And I think most clinicians would believe that the risks of pokes and blood-draws are known, they're quantifiable, whereas the unintended interactions are unquantifiable, and they are known. So, most of us feel more comfortable dealing with risks that we can define and we understand and the rest we don't know and we don't anticipate.

DR. NELSON: Just to follow-up with two observations, I remember interviewing some kids about the risk of research and asking them about the risks of blood test, and a kid

reacted by saying, what risk? The pain is going to happen. It's not as if it's not going to happen or it might happen, I mean, it will hurt.

I mean, he was perfectly acceptable to have it hurt, but applying the notion of risk to that experience was a bit foreign to him, and actually, I think he was fairly insightful on that point. And if you look at in many of the European guidelines, they'll use the term "minimal risk, minimal burden," and they'll make a distinction between--so the blood-testing here, since it's known, in some sense would be described more as a burden, the administration of the drug, since these are probabilities that would involve, would be described as the risk.

So, I only mention that to add some nuance to that observation, but that's where the judgment comes in in terms of proceeding with such a protocol.

DR. GLANTZ: [Off microphone.]

DR. NELSON: Yes, risk and discomfort would be another way, but the notion of burden, which is different than risk.

DR. DASARATHY: Well, maybe I didn't make clear. When I said "risk," I did not mean the pain of the discomfort of the blood-draw. I'm talking about potential vasovagal episodes, potential tachycardia, these kinds. I'm not talking about the pain. You're right. The pain is going to happen. The kids know it, parents know it. It is a known effect. I'm talking about the very unusual risks of vasovagal and any other accompaniments versus the unknown with drug interactions.

CHAIRMAN BOTKIN: All right. So, let me see, give one more opportunity for anybody who wishes to speak to the notion that there are protective mechanisms of some sort that one might utilize with the use of this cocktail as described in healthy kids 12 and older that would bring this within a minimal risk category.

DR. JOFFE: Yes, well, acknowledging what was said about the increased burdens of doing this 4 times in an individual kid rather than once, if I were an IRB and reviewing this proposal, I would want to ask the investigator can you technically and scientifically answer your question by giving 10 percent of these doses of each drug in a cocktail? Are the assays sensitive enough to pick that up? Is there any reason to think that the pharmacokinetics is not linear?

Scientifically, do you need--these are really, I think, low-end full pharmacologic doses of each of these agents. Do you really need that or can you do it with 10 percent, 1 percent, whatever the number might be to get us to a more comfortable range. I think I would feel quite comfortable with a drug cocktail that involved a 10 percent dose or a 5 percent dose of each of these agents compared to what is listed in this protocol.

CHAIRMAN BOTKIN: All right, let's

pick up that hypothetical specifically because I think that's where I at least wanted to go with this, and we could even reduce some of the comments and literature about one-one hundredth of a dose, et cetera. Continue to administer it in an oral fashion and have some limited blood-draws and see how that changes the conversation.

DR. RAKOWSKY: So, just to pick up on Steve's comment, let's say you go all the way down to 1 percent or one-hundredth in the microdosing, would there come a point, because it gets back to the regulatory definition where if you have a healthy child and there's any potential risk, they can't fall into risk level three. It'd have to be a two with potential benefit. Would there ever come a point where you can say this is just a minimal risk? In other words, give him a low enough dose. I'm comfortable enough about unintended consequences, allergic reactions, et cetera.

So, I can call this a risk level one.

I guess for well-established drugs, you could potentially do it at, but for some of the newer things, I mean, I think that's what the question is here.

Is there a certain level at which you can say I'm so comfortable that there is near zero risk that I can do this in a healthy control? Because if it's not a healthy control, then you really can't use three. It has to be the disease condition, so there has to be some benefit there to make it a two.

DR. ZUPPA: In response to that, so say you're giving out one-hundredth of a dose, and it's really deemed no risk whatsoever, but the outcome of that micro-dosing, the plasma concentrations are not measurable because the dose is so low. So, you're doing this study, but you're really not going to glean any information from it. I think so even the risk may be so low, it's still subjecting a child to all these things, blood-draws, just the consent process, the drug administration, for what?

So, I wonder where that line is.

CHAIRMAN BOTKIN: Good. And that would have to be a caveat with whatever hypothetical was that it was sub-therapeutic, but still measurable in a meaningful sense and scientifically for the outcome of the study.

DR. ZUPPA: Yes.

CHAIRMAN BOTKIN: Yes, because, obviously, no point in doing it if it gets too low.

Dr. Towbin?

DR. TOWBIN: I'd like to make a comment about healthy volunteers because in the shop that I work in, which is conducting clinical research, we have a large number of healthy volunteers, and one of the things that's been very interesting about the evaluation of those individuals is how often one has incidental findings that were unknown to the child or parents, things that show up on an MRI scan that were unbeknownst to those individuals. That offering these kinds of

agents would be potentially an interaction that would be adverse to them, and there was no way of knowing that in advance.

If an individual is suffering with a disorder and might get such a drug for medicinal or therapeutic reasons, one might be able to consider and balance those things, but for a healthy volunteer who walks in thinking they have nothing wrong with them and they're perfectly fine, the concerns about unexpected adverse event not coming from the drug, but because of some part of the individual's constitutional so has to be raised. And so, again, it's kind of an issue here for me about what constitutes minimal risk.

CHAIRMAN BOTKIN: Dr. Leeder?

DR. LEEDER: Going back to the issue of dose, I think it's worth bearing in mind sort of where a group might be coming from in proposing to do a cocktail. To my knowledge, there haven't been any four component cocktail studies conducted in children. And so, anybody

who is considering doing such a study will be relying to justify the choice of compounds will be relying upon the only available experience, which would be that in adults. And so, then the question becomes this issue of dose. And so, one would think that the dose that would be used for a cocktail study like this would be the minimum dose required to answer the question or give you the meaningful results.

The problem is we don't know what that is, and so, I think what we're seeing in this particular context is really an arbitrary assessment of what might be an appropriate dose which is not unlike what is done in trying to come up with a dose to treat a clinical condition in the absence of any hard data.

So, my comment regarding the caffeine comes from that the fact that I think that having to drink two cans of Coke back-to-back to get that type of a dose, to me, it seems like a lot. Now, they probably weren't giving Coke as probably a caffeine citrate solution or

something like that. It doesn't matter. But I think when I say that seems high to me, what I'm really arguing is I think you could the study with a lower dose, but, again, I think you could do the study with a lower dose, but there are no data in children to say what's a minimum dose for a study like this.

CHAIRMAN BOTKIN: Dr. Zuppa?

DR. ZUPPA: And I also think it depends--again, the devil's in the details, about the clinical situation. So, 2 mg of midazolam, that would be the oral premed for a kid getting a TNA. So, there's a healthy population right there who has obstructive sleep apnea and tonsillar adenoid hypertrophy. So, the study there, you would not be giving an experimental drug, you would be measuring the pharmacology of a drug whether it's off-label or not, but that is being used as standard of care.

So, the risk paradigm shifts there, and the risks become more of the blood-draws,

and then you can say we're in the OR, you're under anesthesia, you're really not going to be feeling the phlebotomy. We're going to put a peripheral.

So, I think it depends upon the question and the drug and whether or not you can find the setting where it's more easily and appropriately studied.

CHAIRMAN BOTKIN: So, the argument is that there's likely to be clinical circumstances in which children are getting this drug clinically. You just do your PK and pharmacodynamic studies in those contexts and answer the questions without use of healthy volunteers.

Yes? Dr. Rakowsky?

DR. RAKOWSKY: Just to add an IRB perspective, not only is it done commonly, as risk level 1. That's an expedited category. I mean that's expedited category number two. That's so common, that's scenario is set up. I think this question was focusing more on just

de novo, giving these kids a med. Yes.

CHAIRMAN BOTKIN: Dr. Leeder?

DR. LEEDER: And so, just to follow-up on Dr. Zuppa's comment, when one does these studies and is determining that the child is healthy, what you're really looking at from a drug metabolism perspective is do they have normal, hepatic function? And so, you could get this the ontogeny or the pharmacogenetic information or whatever it is if you had probably in the medical record anyway evidence documenting that the child had normal or did not have normal hepatic function, where that sort of healthy might apply.

CHAIRMAN BOTKIN: Skip?

DR. NELSON: Well, you could take Lainie's and Leonard's because I was going to ask the question summarizing and leaving time for questions three and four, just keeping an eye on the clock.

DR. ROSS: This is just an FYI. General pediatricians, we don't draw blood on

healthy children. So, there would not be no LFTs in the chart. We just don't.

CHAIRMAN BOTKIN: Lainie?

DR. ZUPPA: Per-operatively?

DR. ROSS: So, pre-operatively, they might.

DR. ZUPPA: Not necessarily.

DR. ROSS: Right, well, it's fascinating what you meant by "healthy." You actually gave them two diagnoses: tonsillar hypertrophy, obstructive sleep apnea. I'm not sure that's actually "healthy." These people have disorders and conditions.

DR. ZUPPA: So, healthy in the terms of how Dr. Leeder--in terms of drug-metabolizing. I mean, define healthy in this population here. I mean, there, find a child without asthma or OSA or whatever the many diagnoses that we have going around now. I mean, define a healthy child in the general population.

DR. GLANTZ: Well, it's like the

saying that's there's no such thing as a healthy person, only people who haven't been adequately worked-up.

[Laughter.]

I just wanted to comment on the nature of the discussion because he started out asking about minimal risk, and I just want to point out that we went into other stuff. We started the conversation saying soon that this will be useful, right? So, and now we've moved into the question of whether or not it actually is useful. So, we're not just asking the question about minimal risk, we're also asking the question about justification. At what point can you do it?

I mean, the first thing that comes to my mind when I look at this, if we're going to be more concrete, is why are the ages 12 to 21? I mean, why use children at all. That if you can do this in people who are 18 to 21, if you can get the same results, that it seems to me the first rule should be you don't use children

unless you have to. And from what I could see in terms of the inclusion criteria, I don't see any argument for including any children. It might take longer, but that's not an important consideration, I think.

DR. KOPELMAN: That was also my question. If the conclusion was that a control group of young adults would provide an adequate control group of the 12 of age or older group proposed in this study, then why not just use the older adolescents? If it was good enough for the control, why isn't it good enough for the other?

CHAIRMAN BOTKIN: Skip?

DR. NELSON: Well, Jeff, I guess let me make one comment to Leonard's point. I agree with your observation. There is a sister agency whose policy is to include children unless there's a reason to exclude them, which is the opposite view depending on how you interpret that policy. Although, fortunately, children are defined as including 18 to 21,

which gets you out of that dilemma.

But, Jeff, a lot of the questions people have raised, I'm thinking about the assent, permission, other things, it really goes into some of the other ethical issues that are important to this beyond risk assessment, which is really Norm's question. And Norm's raised a number of critical comments about the oversight system, which is really question four, and I just wanted to make sure we leave time to hear those discussions, which would be certainly of interest and whether you think-- because I'm beginning to hear similar themes sort of over and over again, at least in response to this question.

So, unless you want to try and summarize, or it's up to you as the Chair. I don't want to step on your toes too hard.

CHAIRMAN BOTKIN: All right. Point taken. Let me see if there's any further comments about the scenario in question two that people want to speak to before we have an

opportunity to move on. And I do agree there's been a mix of concerns, and some of it still has to do with the validity of the science or the social value of the science, and, perhaps, folks are struggling with this in part because they have yet to be convinced that this form of research is of critical importance to the welfare of kids.

So, that's a piece that's still sitting out there. But also hearing a fair amount of hesitancy at least in the context of this particular protocol with these higher doses of considering that to be minimal risk, I don't think at least I heard clear answers so far about the circumstance in which those doses were significantly reduced. And, of course, you can do a reductio ad absurdum and talk about 100 molecules being administered and what's the risk associated with that, but we haven't gone there.

So, I think to my mind at least, an element of uncertainty about the risk

assessment for these lower drug doses.

So, let's look at question three then. And I'll go ahead and read it for us, and Skip, perhaps, can put it up on the slides for us.

There are other issues beyond the assessment of risk that may enter into the judgment about the ethical acceptability of a given clinical investigation, such as the scientific merit of the protocol, social value of the research, skill and experience in the investigators, or the potential for exploitation of economically-disadvantaged populations. Please discuss how these, and other relevant ethical considerations would factor into a decision to allow an exploratory IND trial to proceed. In your discussion, clarify any differences in these considerations between a population of children with a disorder or condition and a population of normal, healthy children.

So, again, we're moving beyond the concept of risk per se and want to look to

other factors in assessment of a protocol that may influence acceptability.

Dr. Zuppa?

DR. ZUPPA: Hi. And I think what I mentioned earlier speaks to this question. So, in the hypothetical protocol, and Dr. Leeder actually commented to this earlier, as well, getting the information in that control group, I think the scientific merit of the protocol is important.

If in that hypothetical protocol answering those questions would prevent the need for other PK studies, I think there's more scientific merit. If it was more of an exploratory study and regardless of the outcome we would still want to do further PK studies in that subpopulation of sick patients or children, what did it add to our general knowledge? How did it help us? Did it really help us in our dose selection? So, I think the scientific merit of the protocol is important.

And then I think going to control

subjects. So, say there is a difference of the PK in the control that the "healthy children" versus the children with the illness, is the question to establish dosing guidance in that ill subpopulation? And if that's so, although it may not be generalizable to the other populations, it's still very, very relevant to that specific disease population. So, what the added data of the healthy controls gives us, I think, is in question. I don't know if that was clear.

CHAIRMAN BOTKIN: Norm?

DR. FOST: A minor and major point. The minor point is, of course, all those other things matter. The scientific merit, the social value of the research. We talked a little bit earlier about is this really, really critical that we do this research now? Are lots of children are going to die? No. Is there an advantage in doing it? Could we practice better medicine? Yes. So, I mean, all those things matter.

But I want to get to the exploitation of disadvantaged populations and say it's a point that gets back to the package deal issue, but exploitation is another one of those words like coercion, that Steve correctly pointed out a couple of hours ago, is misused and has an inflammatory tone to these discussions, and appropriately. And this is one, also. That is, there's good exploitation, there's bad exploitation.

I'm a pediatrician, I see kids whose parents are worried and anxious and fearful. I exploit their fears by saying hey, guess what, I'll do a history and a physical and order some lab tests, and I'll either reassure you or I'll find out what's going on, and I'll "make a lot of money." I'm exploiting their need, but in a way that's quite ethically appropriate.

Oncology researchers exploit dying patients. You're dying, you have cancer and you're going to die. I'll tell you what, I have an NIH grant, you come join my study, I'll

get refunded, blah, blah, blah. That's not the language that you use, but that's what's going on. It's not an ethical problem if it's a well-designed study, it's well-reviewed, there's good standard for consent.

So, those are examples of good exploitation.

I want to give one more example, and this is fanciful, but it's to make this point about the package deal. If you have a normal child, a healthy child, and he's impoverished, he's barely getting food and he has no prospects for education, blah, blah, blah, and I'll give you \$1 million if you'll let me just do a little pharmacokinetic study on him with a few finger sticks. Is there a direct medical benefit for giving him \$1 million? No. Is this a problem? Is this un-wrongful exploitation? Should--huh?

DR. GLANTZ: It is wrongful.

DR. FOST: Well, I respectfully disagree. If I'm the parent of that child or if

I'm that child, if I'm a fierce advocate for that child, it sounds to me very patronizing of you and others to say no, I forbid you from entering into this deal to help your kid have a life that he otherwise would have no crack at, at all, and to prevent him from all the harms of his poverty.

So, there's lots of things we do that it would be better if we lived in a world in which these questions didn't have to arise, but to say that it's prima facie wrong to offer a kid, just a kid, not the parent, the kid a deal where he is unquestionably going to be much better off and be relieved of unimaginable suffering, and the only consequence is he's going to have a few drops of blood drawn from his finger, that this violates some important moral principle, I don't get it.

CHAIRMAN BOTKIN: Leonard.

DR. GLANTZ: So in terms of coercion or exploitation we can talk about what those, you know, what exactly those words mean but,

you know, the free market doesn't work all of the time. So, there's no reason not to take the kidney out of the kid, too. You would still say that's not exploitation.

DR. FOST: I disagree.

DR. GLANTZ: No, I understand. But I'm saying, it would not be dis-ploitation. We're just talking about the amount. So with would that kid be better off with \$1 million and one kidney? Absolutely. And that's your standard for exploitation.

The issue for exploitation isn't so much with what somebody would consent to, but what we allow people to ask of people and that's the nature of exploitation. So that, we--you know, one of the things looking at consent and all of this stuff is that we focus on only one half of the relationship and the half is the subject or the person being asked. We don't look at the morality of the person doing the asking.

And so, you gave a couple of other

explanations of what you thought exploitation is and one of them I think is and one of them I think isn't, but we could go into those details later if you want. But, I think, what we're talking about, just like the word "minimal risk" doesn't really haven't much use and the word "minor increase over minimal risk" doesn't really have much use. We're talking about value judgments. And we're talking about using people because of their social situation, their poverty, their racial situation, or that we wouldn't otherwise use those people.

So you can get people to do anything for money, I mean, that's why there are minimum wage laws and the reason why there are minimum wage laws is because people would be exploited because they really don't have much choice.

DR. FOST: Minor footnote. All Blue Collar workers are exploited. I mean, people wouldn't choose

DR. GLANTZ: [Off microphone.]

DR. FOST: People in Appalachia would

rather be doing other things than working in a coal mine if they had other options, but they don't. And to say it's immoral exploitation to offer them a job in a coal mine with as much safety as we can put into it and a reasonable wage, is to me, inconsistent with how the system works.

DR. GLANTZ: Yeah, I'm just saying using the word exploitation in that way means that the word has no meaning. It means that anytime anybody is induced to do something is exploited, is just wrong. That there is a difference between people being induced to do things and people being exploited.

CHAIRMAN BOTKIN: Well, let's see what we mean in this particular context though.

[Laughter.]

CHAIRMAN BOTKIN: I think the context we're speaking of here isn't so much one in which we're trying to trade some small benefit for risk of great harm. In this particular context, the general theme has been no prospect

of direct benefit to the kids, and so, we want to think about who it is that would be vulnerable in this type of research and how might we protect them from that sort of vulnerability if we stay on this exploitation theme. Skip.

DR. NELSON: Yeah, let me concertize, if you will, that theme and I enjoyed hearing this conversation because I actually anticipated that throwing this phrase into this question would be like red meat to the two of you.

[Laughter.]

DR. NELSON: So, let me concertize it. Consider a study that is not hypothetical, an IRB which is no longer in business, approves a PK study of a drug for asthma in kids without asthma. Using the argument that, in fact, they're seeing a doctor so there is direct benefit to them for being in that trial. So package deal issue.

And then, on top of that it involves

an overnight stay and they are children, I think it was the age of 6 to 12 and they paid the parents \$500 to put their kid in this facility overnight. We don't know if the parents stayed there or not. And the location of the facility was basically East Los Angeles.

So, behind this question, there has been some literature written on guinea pigging in the adult world. People who make money out of becoming healthy volunteers and we do have child labor laws, so rather than the minimum wage, we do have child labor laws. So this is really what's going on. If we broaden this, particularly to include healthy, normal children to what extent are we really opening up that Pandora's Box, if you will, to those kinds of concerns.

That's the intent behind this. In a practical matter, what would we think about those sorts of issues going forward?

DR. FOST: And is there something uniquely relevant to this type of population of

kids vulnerable that wouldn't be true in the broader research context?

DR. NELSON: Well, it's hard to come up with data, but I think qualitatively it would appear to be somewhat different if one is at least going into a population with a disorder or condition about which that research is relevant, maybe not immediate needs because there's no prospect or method, but perhaps future needs in a much more relevant way as opposed to simply serving as a subject in a study much like we allow adult, healthy volunteers.

So we've not--this is really pointing to a line that at this point in time we've not crossed in the course of drug development in saying "Here's the line." What are the issues if, I'm not saying that we will, but if we decide to cross it.

DR. FOST: What is the line that we haven't crossed?

DR. NELSON: The use of normal,

healthy children in drug development in early phase trials.

DR. FOST: Oh. We certainly have crossed the line of offering disadvantaged people material benefits to help advance knowledge.

DR. NELSON: I agree. And the issue of undue inducement is a broad one and unabashedly, shameful self-interest, there will be a publication in the American Journal of Bioethics, precisely on that concept co-authored by me with Tom Beauchamp on voluntary consent. It discusses that. I personally don't think incentives are necessarily an undue inducement but they may raise serious issues of justice.

So I mean, that's, you know, this is what it's really about. So that's what I'm trying to get a discussion on.

DR. FOST: Yeah, so to respond to your asthma example just because I said there's good exploitation and bad exploitation. Obviously,

I don't think all exploitation is good. I think there are good and bad examples and in case it depends on the facts of the case. I might need a little more detail about exactly what was being done to the kids and what the likely risk of this drug was and what was going to happen to them in the hospital and how seriously assent was taken so if the kid really didn't want to do it, he didn't get to do it, and what's the \$500 going to go for.

So there's--I'm not sure I'm going to vote for that protocol if I'm on that IRB and I'm not sure either if I'm critical of them. I need to know a lot more. But I wouldn't just rule it out because it's a healthy kid.

CHAIRMAN BOTKIN: Loretta.

DR. KOPELMAN: Yeah, I'll say something about the issue of disadvantaged groups. I'm assuming that most of the children with non-alcoholic or young adults, non-alcoholic, fatty liver disease or obese, so you could say well, there's more obesity in the

poor part of D.C., in certain parts of D.C., so maybe we'll recruit from that area and give a monetary benefit to the parents and we'll learn something from these children as a group.

But the problem is, fortunately not all children in that area are obese, and many of the children in the suburbs are obese. So if you focus on this particular group, then I do think you--because recruitment is easier because of the monetary package. You are exploiting them because others will benefit from that data beyond this group and some of the people in that area of D.C. are not going to benefit at all.

So, I think there is a danger when we go to other things like monetary benefits that we will exploit certain populations.

DR. RAKOWSKY: [Off microphone] --the investigators, I don't want to stop this chain here. So, once this is done.

CHAIRMAN BOTKIN: Other comments about exploitation? Larry.

DR. GLANTZ: Yeah, I think that when we pay people we should stop calling them volunteers. I think we should call them employees and that volunteers are something else.

It's also hard to think of, you know, again, young children as volunteers. They may be normal controls, but they're certainly not volunteers. If anything, their parents are volunteers.

The other thing, that in terms of undue inducements or even the term exploitation, I think that other than economic exploitation, that probably the parents of the sick kids are easier to induce than the parents of healthier kids because of their false notions of benefit or getting their care attended to better. So, I think probably the most high-risk people are the parents of, you know, terminally ill or very sick children. They'll do anything, because they are desperate.

So the question is what make a parent who ordinarily has to serve a protective function, say sure, you can give my kid benzodiazepines and caffeine and all that. Why would a parent do that if they, you know, purely on a volunteer basis for a young child?

CHAIRMAN BOTKIN: Steven.

DR. ROSS: So can I answer that? Parents don't-- [sound drop due to sound technician controlling microphone feedback] -- doctors and researchers and you wouldn't directly harm your patient, and I trust you and you just told me it's minimal risk. And what you mean by minimal risk and what a parent means by minimal risk aren't necessarily the same.

I think it's pretty obvious why parents can be, in a sense, cajoled, enticed, induced, whatever word you want, to participate. Actually for very little.

DR. GLANTZ: So I think it depends on the circumstances. I certainly agree that when

the doctor goes from being a doctor to a researcher, that that change in relationship is not at all apparent to the parent or to the child or even to adult patients, when you have that chance. But with this group of kids that we're talking about, in the study they don't have doctors. I mean, these aren't their doctors who are doing this to them. That someone, again, I don't know where these people come from but someone has to produce these 12 to 21 year olds to do this who aren't seeing their doctors.

DR. ROSS: But they come to a doctor's office or to a hospital. They come exactly to the same place.

DR. GLANTZ: Why? That's a recruitment issue.

DR. ROSS: Well, but no. That's my point. They don't see it as different. If you had a place that said, "We are the experimental guinea pig farm, please come." You're not going to get these same volunteers.

DR. O'LONERGAN: I think--

CHAIRMAN BOTKIN: Terri you had
comment on this issue.

DR. O'LONERGAN: I think parents make
a lot of decisions about what their kids will
do and what risks they will be exposed to for a
number of reasons.

Helping other people with disease
might be a reason that a parent said, "Well,
I'm going to allow my child to be exposed to a
certain level of risk because it helps my
cousins or their friends," or whatever and I
think parents do this. I let my children do
things that were risky because it would make
them better people, so we want to instill
altruism, perhaps.

But there's more than just the risk
benefit in a parent's mind.

CHAIRMAN BOTKIN: Steven.

DR. JOFFE: So, five or 10 minutes ago
Skip talked about not having crossed this
particular line before, moving from the

affected population of children with the condition to the healthy volunteer population. And I've been struggling with to sort of defend that line in my mind.

in other words, why are we so reluctant to cross that line? Why are we so comfortable--not comfortable, but why are we more comfortable exposing a set of children who have a condition to a set of risks when we have no expectation that they will benefit from that particular exposure.

And then, on the other side of the line we have children who we can't say have that condition and we are so unwilling, so much more relatively unwilling to expose them to that same set of risks. And I'd love to hear theories on this. It strikes me that the probably the philosophical answer has to do with the kids who have the condition having some stake in that knowledge, that the kids who don't have the condition don't have. And so, maybe that justifies that difference.

Although, I think one could argue about that.

I think more practically speaking, the reason why we find ourselves more comfortable being willing to expose kids to risk without the prospect of drug benefit when they have a condition because it allows us to operate under a therapeutic misconception, both ourselves as investigators and IRB members and also, it's easier for parents and older children to hold those therapeutic misconceptions when they enter into those sorts of trials. And if that's really the reason behind it, then I think it's a very hard reason to defend. It's very hard to defend that particular line if that's what underlies our drawing of the line.

Even the more philosophically rigorous distinction of kids with a condition have a stake in the outcome of this particular study that kids who don't have that condition don't have, I think could be challenged. Might we enroll healthy volunteer siblings of kids with the condition, because they have a stake by

virtue of their family relationships and the knowledge.

It seems to me at least plausible that we could revisit that and if we'd be willing to so that with them, what about just healthy kids pulled from the general population.

So, I'm struggling to defend why we have this line that we won't cross and really therefore why the distinction between 50.51 and 50.53. Why in one situation is the limit minimal risk and in the other situation the limit is minor increment over minimal risk. Even if we could define the boundary between those two risk levels.

CHAIRMAN BOTKIN: Good, and I think that goes to the structure of the regulatory scheme itself, which a number of folks around this table have written about.

Norm I think is next and then Leonard.

DR. FOST: Yeah, I'm, glad Steve reminded me about the healthy--the sib of the kid with the disease, the healthy sib, because

it dovetails with sort of what I was about to say anyway other examples in which we allow invasions of children's bodies, these healthy children with no direct benefit to them.

So, for example are we force--I mean instruct them to do things that are not in their direct benefit. So for example, parents are entitled to teach their kids altruism, kids who are old enough to understand what that means. You're going to shovel the neighbor's walk today. We're going to go on the community fundraising drive. We're going to do something instead of go to the ballpark or something like that.

Similarly, a parent might appropriately say we're going to donate blood today, you and me. And if the kid's old enough, the parent--we don't think it's evil or wrong to drag the kid down to the blood bank, if he's old enough to give some blood. No direct medical benefit from him. No financial benefit, but just teaching him what it means to

be a part of a community.

So, where is this important line if you agree that's okay. The third example that I was going to mention, is we ask kids to donate bone marrow and kidneys to their siblings or to other family members with no direct medical benefit. We say it's in their psycho-social benefit.

And I agree with it. And I've written about it and I've testified in court about it and I think it's okay. And we now do it thousands and thousands of times a year. Far more risky, far more invasive than some of these studies that Dr. Leeder is talking about.

So if all of those things are okay and aren't crossing any really important moral line, where's the added evil or sin in saying we're going to ask you to undergo a few finger sticks to advance knowledge at very low risks to help the community.

So, I want to point out I'm talking out of both sides of my mouth here, because

Skip has asked for relevant points to consider. So, I think that exploitation is not a relevant point to consider, bad exploitation is. I think the package deal is not a relevant point to consider. I think it's a good thing, a package deal That's all--those all points in favor of doing more of these studies.

On the other hand, I think taking assent seriously is also important and that would slow all this down quite a lot. And somewhere in between is this altruism issue. That is a parent might say, "I don't care whether you want to go or not. We're going to shovel the neighbor's walk today or we're going to donate blood."

So these are all--Skip allows me get off the hook because he asks for relevant variables. So I think these are all things that weigh on one side or the other of this debate, that should all be considered. How it would come out on balance depends on the specific proposal before us and all the facts

of the case.

CHAIRMAN BOTKIN: Leonard.

DR. GLANTZ: Yeah, I really want to talk to Skip, but I just want to make one comment and that is so far no court has permitted parents to take the kidneys out of a healthy kid and give it to a researcher.

DR. FOST: What?

DR. GLANTZ: And give it to a researcher.

DR. FOST: Oh, sorry.

DR. GLANTZ: Even though it will help all kids, not just those individual kids and you find that to be fine. That they should be able to give it to researchers, I assume.

DR. FOST: No. No.

DR. GLANTZ: Oh, no? Even though that's a psycho-social benefit?

DR. FOST: That's too far.

DR. GLANTZ: Oh, I see. Okay, so--but anyway I really want to talk to Skip, because I think you're absolutely right and the way I

come down on it is that the fact that a kid is not a healthy volunteer means that they should be getting more protection, not less protection.

I come down quite differently on the-- you know, the procedures need to be commensurate with the kids would ordinarily get. Because I think the fact that you get bone marrow aspirations doesn't mean you should get more. I think that does mean you should get less bone marrow aspirations. I think the difference for me from time to time is that the kids who are ill will have procedures or get medications that you could then sort of piggyback on, if that's the right thing. Blood will be withdrawn, you can take a little bit more blood. A drug will be given anyway and you can do the pharmacokinetic study on the kid.

So to me, that kind of factual difference makes a difference and it's interesting to see it come up in IRBs, because

you will see normal volunteers, people who are normal volunteers, the researchers will say, "We should pay them \$50." And then there are people in the hospitals they're going to do additional things to, but they say, "We're not going to pay them anything." And the question is why not? That's--they're also normal volunteers for this purpose, even though they look sick.

So I think there are definitional and also sort of socio-cultural issues that have to be overcome, but I would not assume that the fact that a kid is sick, you know, means there not that same kind of line.

CHAIRMAN BOTKIN: Lainie.

DR. ROSS: So all three of us, you've got three ducks in a row in agreement here.

Actually, we actually have across the table because since Skip and I have actually written on this topic specifically saying that we should really be able to meld the two together. That you really can't justify

placing children who have a disorder or condition at greater risk. Whether they need greater protection is probably a harder argument to make, but clearly, we would all say they shouldn't be exposed to greater risk.

CHAIRMAN BOTKIN: Okay, we have Loretta and then Skip and then we want to try to move onto Question 4.

DR. KOPELMAN: I think when this question is considered, people usually go one of two ways. They say okay, increase the risk level; minor increase over minimal risk for everybody, healthy or nonhealthy subjects. Or they go minimal risk for all. Some of us have gone one way and some of us have gone the other.

I would argue that we have had two courts say that you have to keep the risk at minimal risk for children who are in research. I think you can--you can make a consistent picture here and say that the risk level has to be minimal risk for the children with

conditions, but no greater than what would be a minor increase over minimal risk for healthy children, because the risk for the children with conditions it's going to be relative to that condition.

So, I think it is very important that we try to come up with a consistent picture, but there's a genuine disagreement about how to do that.

CHAIRMAN BOTKIN: Skip.

DR. NELSON: Just one comment and then I'd like to ask Norm a specific question.

So the article that Lainie and I co-authored, I must confess was in my pre-FDA times and at this point I'm interested when we get to Question 4 about whether one could operationalize what we had suggested in that article.

But Norm, I have a question about this assent issue. I mean, this assent issue has been around for years. Bill Bartholome argued that assent need to be respected. Ramsey felt

that there was no benefit for parents to allow their kids to go into research that didn't offer any prospect of direct benefit. He later admitted in a less well-known piece that the moral benefit of teaching altruism that Bartholome argued for could potentially be a benefit that would justify a parent allowing their child to, you know, participate in minimal risk research. Whether that's being dragged to the blood bank or down to the researcher's lab to have a blood test.

But earlier, you had pointed out that a lot of these metabolic issues pertained to kids who are under a year of age and, you know, whether up to two, three, or four and suggested that you could have what some might call behavioral dissent, basically withdrawal and crying upon pain. So my question to you as an IRB chair for 20 years, how did you approach the waiver of assent that one would be allowed to, as an IRB, in other words if that--if it was a neonatal blood test an assent can't be

given. I mean, how did you square your regulatory authorities as an IRB chair with your ethical arguments that you're offering here about honoring assent?

DR. FOST: Easy. Because I was chair of the IRB, I wasn't the IRB. That is, I would argue very strenuously against some studies of this sort for reasons that I've said and I would lose. I mean, I would get outvoted 15 to 1. I was actually a nonvoting member. So that's easy.

And this will lapse into Category 4, but an example of how far afield we've come from minimal risk as one of the perimeter defenses. We sat in a room, you and I sat in a room like this a year or two ago about a proposed study on non-therapeutic brain biopsies in children. And I use non-therapeutic brain biopsies when I give my lecture on this topic as something that was actually proposed at a meeting at Harvard in 1971.

Just as an example of how badly the Common Rule was needed. I sat in an IRB at Harvard in which they approved non-therapeutic brain biopsies in kids with developmental disorders without 10 minutes of discussion. I'd use that as an example of how IRBs were not working, but it wasn't--I'm not now talking 1971, I'm now talking 2009, where a group of very sensitive, thoughtful, caring people and I think the majority voted. It was either outvoted--I mean, they voted for it or it was a very close vote. But a lot of very thoughtful pediatricians thought doing non-therapeutic brain biopsies in a particular group of children was just fine.

So this notion that we're protecting these people with standards of medical risk, parental assent and consent, and all of this stuff is far-fetched.

CHAIRMAN BOTKIN: Leonard.

DR. GLANTZ: I was at that meeting, too. And what struck me about that vote is

that everyone who was in favor of doing unnecessary brain biopsies on kids were physicians and it was a close vote. And there were physicians who joined the opposition and that goes to the procedural question of who should make these decisions? And I would not leave it up to physicians for exactly that reason. That the empirical reality is that people who do brain biopsies for a living should not be asked if it's okay to do it. All right? And that people whose career depends on doing brain biopsies should not be allowed to ask if it's okay to do it.

And so, your procedural point, I think, is well taken. I don't think that IRBs can't do it; I think many don't it, and one of the reasons is that they are full of the wrong people. But that you could have review committees that actually do do it. If the doctors were excused from that meeting, you would have had a different outcome. And because they were taking into account very

different considerations. But I'm not disagreeing with you that IRBs, many IRBs don't do a good job. It doesn't mean that they can't do a good job.

CHAIRMAN BOTKIN: I was at that meeting, too.

UNIDENTIFIED SPEAKER: So was I.

CHAIRMAN BOTKIN: And my recollection --that's right. It had less to do with who is an MD, but it was clinicians caring for these kids who tended to be the ones voting in favor, whereas those with an ethics background tended to vote against whether or not they had MDs or not.

All right, I think we need to move on to the fourth question here. We've got about 25 minutes still. So, let me go ahead and read that.

It's well-documented variability and deficiencies in the system of IRB review of clinical trials. In light of the discussion of the above questions, how can we assure that

children will be adequately protected if we allowed for the broader inclusion of children in exploratory IND trials?

Alex?

DR. RAKOWSKY: I was going to bring this up with question three, but it sort of segues here. PK/PD studies, we do a lot of them at our institution; are not as easy as people claim they are, and Dr. Leeder is a good example of having to do things properly. I mean, it takes time, timing, micro-assays, proper tube collection, et cetera.

So, I think one thing that IRBs in general can look at is: Is this a study that's being done with a well-known consortium that has its logistics figured out? Because the last thing I want to do is I'm going to enroll these kids into the study and then get zero results back or incomplete results back. So, I mean, that's almost unethical to then allow that study to kind of move forward. So, one argument is to sort of have consortium studies

where we have a well-recognized group actually setting this up and doing it properly.

CHAIRMAN BOTKIN: Steven?

DR. JOFFE: I actually have a question that maybe Skip or Michelle can answer. When the FDA gets an application for an IND, whether it's regular IND or an exploratory IND in a pediatric population, in deciding whether or not to approve that IND application, are the reviewers looking at the subpart D criteria and making a judgment that, in their opinion, the study is approvable under one or more of those categories or are they approving the IND completely independent of any attention to subpart D and figuring that it's up to the IRB to make that determination?

DR. NELSON: Just recently, I think probably on the order of six weeks ago, we did what's called CDER Rounds, which is Wednesday afternoon rounds within the Center for Drugs, and the specific topic that I presented was the relationship between the clinical hold criteria

and subpart D, which is what you're asking. So, when an IND comes in, what are the criteria in which an FDA can say no, stop, redesign, do something differently?

The clinical hold criteria basically say for Phase 1, if it's an unreasonable risk, and Phase 2/3, so 1/2, unreasonable risk, Phase 3, that includes unreasonable risk, but also would--it's not designed in a way that would answer the question. So, an issue of scientific design.

The basic argument that I presented, which I think was well-received and generally accepted--although subpart D is not explicitly written into the IND regulations under 312--it's that one can interpret subpart D as framing what it would mean to be an unreasonable risk. In other words, if one is not in compliance with subpart D, that that could be framed as meeting the unreasonable risk category for a clinical hold. Can I assure you that that always happens? No. But

I feel optimistic that that, in fact, is the way that things ought to be, and, hopefully, if there's variance from that standard, that that standard could, indeed, be addressed and corrected.

DR. GLANTZ: [Off microphone.]

DR. NELSON: Subpart D was accepted and approved the FDA, adopted in April of 2001. There hasn't been a pediatric ethicist in the FDA until 2003, when that was required under the BPCA. So, I think that, in all honesty, it's been an educational effort and some change. I wouldn't want to say that that's always been true, but I feel confident that it is increasingly true and will be even more true in the future.

So, but I don't want to overstate it, so it's really a yes with a but, that there's still--these INDs are still reviewed by 17 divisions, by 3 different centers, and whether everybody is cognizant of subpart D and how that might apply to a pediatric IND, I cannot

at this point with 100 percent confidence say that that's the case.

DR. JOFFE: So, I take it from your answer that even though much of the time, most of the time that implicitly or explicitly has been part of the reviewers thinking that an IRB receiving an application where an IND has been granted should not assume that that judgment has been made by anybody at the FDA and should assume that it is, in essence, starting from scratch in trying to answer the subpart D questions?

DR. NELSON: I think as a default position that that should be correct. I will say that the only circumstances to date where ongoing trials have been subject to retrospective clinical holds because of subpart D issues have been when I have been called by an IRB that have raised concerns. And then I looked into it.

DR. DASARTHY: Yes, I don't know that

it has been said, but extending on some of the things that have been said, is it possible that when it comes to children, make sure that the consent is done by somebody who was not directly involved in the care of these children, because as Lainie said, when patients come to us and if I tell them this is a good study, you should consider it, they don't hear that. What they're hearing is my doctor's saying do this study. So, they'll say okay.

So, what they hear is not necessarily what we are saying when we are also having dual charge of clinical care, and this becomes even more of an issue when the pediatricians are telling the parents because the parents are completely dependent on the pediatricians to take care of their kids, and when the pediatrician says something, it's very hard for them to say no, even though there are all kinds of disclaimers. We say that it will not affect your kid, it will not have any influence on their relation, but they don't hear any of

those things. And we have had this that on the day of the study, I've gone and said that do you really want to do this study? They say, well, you told us. I said, no, I said this. They said, do you have an option you can stop now? They say, can I really stop now, and we have stopped it.

So, maybe it would be a consideration, especially in this well-known population to see if people who are not directly giving clinical care are involved in the consenting process.

CHAIRMAN BOTKIN: Dr. Zuppa?

DR. ZUPPA: Going back to having consortiums and experts in the field, I think recent advances in pharmcometrics, so modeling and simulation techniques, Bayesian pharmcometrics using priors established in the adult population, such as clearance and line of distribution. All of those can go into more optimal trial designs and dose selection for prospective trials in children, and I think including a more rigorous design methodology,

including simulations, could be something that could be used to protect children. You can account for variability in pharmacokinetic parameters in adults and really kind of get a better idea of where to start with.

CHAIRMAN BOTKIN: Institutions, do you think, typically have the right people that would be able to support the IRB in helping to make those sorts of determinations?

DR. ZUPPA: I can't speak to all the institutions. I know some institutions do. But there's absolutely the ability to consult out to institutions that do or are independent organizations that do. I know from what I understand, pharmcometrics, I'm involved in the field, and it's a growing field. So, I think that there are more opportunities out there to do more informed trials and actually do more specific PK sampling, which sparse sampling strategies in pediatrics, which you'll need to ensure meaningful outcomes.

CHAIRMAN BOTKIN: Dr. Towbin?

DR. TOWBIN: I hate to be nihilistic, but I think this question's a little bit of a non-sequitur, although it attempts to relate to the above questions. I think that the reason I regard it as a non-sequitur is that I think we acknowledge that there are problems with IRBs and the way in which determinations are made. I don't think that changing the risk levels of how we think about things will either repair that or have any bearing on it. I don't think that IRBs will be worse for a decision that might come from this.

I think the problems in variability, the kinds of political and social networks that populate IRBs that sometimes lead them to problematic decisions, the ways in which sometimes there's a focus on very concrete or minute details to the exclusion of the broader issues. Those things won't be repaired by any decision we make about risk levels, and so, I think there are problems, and I wish there were ways that we could assure higher-quality

reviews from IRBs, and I don't mean to say that they're all terrible, but I agree that there's a problem in the system. I just am not sure that keeping things stringent is an assurance that things will be okay, and I'm not sure that loosening them is like the Oklahoma Land Rush.

CHAIRMAN BOTKIN: Skip?

DR. NELSON: Let me ask a specific question. I would be interested in people's feedback on this. You've talked about the importance of the scientific merit of what's being proposed. You have in front of you a consultation that was done internally by our Office of Clinical Pharmacology that basically said that the normal control group was scientifically unnecessary, and that that was a protocol that was, in fact, reviewed and approved by a local IRB. And many IRBs are going to the point where they've divided (in accordance to the Medicine recommendations) scientific review from the IRB or ethics review

to where there's a two-step process.

So, part of my question here is less, if you will, about the IRB system, because we're not going to fix that in 15 minutes, and we could spend a long time talking about those issues, but specifically, how would one address evaluation of scientific merit under these circumstances? Are there recommendations that one could put into place that would make sure independent of the risk assessment that at least what's being done is of scientific merit?

CHAIRMAN BOTKIN: Norm?

DR. FOST: A couple things. First I just wanted to endorse the comments that were made about some more neutral consent obtainer than the investigator. Somebody who has a grant to study this stuff obviously has a very vested interest in recruitment and so on. So, having some more dispassionate intermediary would be helpful. Use of interactive computers here could be help and not used enough, and there's some good work on that.

But to get to Skip's question, I've become more enamored in the last few years about central IRBs or central review processes. I was opposed to them for 30 years, but becoming more and more enamored, based in part on good experiences with NCI, IRB, Western IRB, despite being a commercial IRB, I think does a very good job. We've been using it. VA has now a central--there have been some very good examples of it, and one of the reasons they work better is because if the right people are appointed, you can get a really good group with good scientific credentials, as well as good ethical input and so on.

The RAC is an interesting example of having a very good central, scientific view of gene therapy of gene transfer protocols, and I think that's worked well, and nothing crazy has gone on in that field since forever.

DR. ROSS: [Off microphone.]

DR. FOST: Huh?

DR. ROSS: [Off microphone.]

DR. FOST: No, since the RAC became effective a long time ago. But I'm thinking, and the other analogy I was going to make is the suggestion that several in the room have already made, that the Pediatric Ethics Subcommittee and the 407 experiences, as few as they are, are a helpful database of what's okay and what isn't okay and what's lacking in this field or what would be helpful in this field is to have a case law; that is to have examples of--so to use this specific topic we're talking about today, is to have some high-quality review of some of these studies of the sort. We've heard that attracted wide support is being scientifically important, scientifically well-done, and ethically okay, and others that were not okay and others that maybe reasonable people disagreed about.

So, I'm just encouraging you to think more about having some review body, some expert panel that reviews these things. Maybe it's an advisory thing like the RAC is. The RAC

ultimately has no power, but it has, I think, a lot of influence. As you say, it has no authority, but it has considerable power.

So, having something like that so that people around the country aren't relying on their local IRB, which almost never will have the kind of technical--I mean, the sophistication of the discussion we've had today will exist nowhere else. So, having some group like this that has an opportunity to review it, even if it's only on an advisory basis, puts it on a Web site, here's some studies, here's how Burckart answered this question, and here's how Jones answered that question, here's how the committee answered this question. I think that might be a useful model to explore.

DR. NELSON: And just to follow-up, there is a proposal floating around in a manuscript that's not yet published about the possibility of NIH study sections serving that role.

Is that someone you would put in that place? And I'm setting a trap here. So, be careful.

DR. FOST: Yes, my problem with study sections is that they're hostages to the one and two primary reviewers. That is, one person who starts off with a negative view of the study and it's dead in the water and not enough people in the room have read it carefully, and the opposite can happen, also. So, even though they're committees and they're well-constituted, and I think they're very thoughtful people, they don't have the kind of collaborative--

DR. NELSON: Okay.

DR. FOST: --really careful discussion that occurred here today.

CHAIRMAN BOTKIN: Okay, Alex?

DR. RAKOWSKY: Just from a central IRB sort of view as an IRB chair, it's a lot of work to set those things up, and I think the CIRB has worked phenomenally well for NCI. But

I think it would be hard-pressed to set up the central IRB for various sort of disease mechanisms.

Maybe one proposal, if you look at the pediatric studies that are being done, about 95 percent of them are being done at 50 major academic pediatric centers. Maybe have those centers come up with a list of experts. We have experts in the following 10 or 12 disease entities. And then if your center is working on a protocol, feel free to then objectively pick from that list. In other words, have an outside consultant.

And I wish I had a list sometimes for some disease entity where we a expert in a field, and I would love to, for example, go to University of Maryland, and say hey, what do you think about this cardiology proposal? And we don't have that kind of mechanism now. It would be almost like a hybrid of a central and a local, where you would just tap into other people's expertise, and that may be something

where we could have it set up, and as a consultant level, so a lot of this kind of legal maneuvering that you have to do with your legal folks without having FWA and all of those kind of things involved.

CHAIRMAN BOTKIN: Okay, I think Dr. Leeder was next.

DR. LEEDER: As an individual who has sat on study sections, I would have to say that spending five hours here has made me well aware of the fact that I'm not a pediatric ethicist, and whereas I may have an appreciation for the issues regarding the scientific merit of an issue, that doesn't necessarily translate in being an expert on conducting all types of clinical studies or studies involving drugs in children.

And one of the things that strikes me when I look at Dr. Burckart's assessment, I mean, the concluding paragraph is the control population and these type of drug metabolism studies is essential for interpretation, but

then he goes on to say that a different control population is adequate for studies. So, one of those seems to me to be a question of scientific merit and the other is one related to pediatric ethics.

And there are a couple of thoughts that have been going through my head as I listened to all of this discussion, and one is the fact that I'm not sure that a population of even 18 to 21-year-olds is necessarily going to be a good surrogate for a population that will consist of 10, or 2, 3, 4, and 5 individuals. And actually I was turning around a question that Dr. Joffe raised, and that is adult IRBs seemingly don't have any difficulty with cocktail studies in adults because they've been done with various cocktails, some of which include a single dose of warfarin on many continents.

And so, I'm kind of asking myself a rhetorical question: If we step back from 21 and above to 20 to 19 to age 18, 17, 16, 15,

how far do we go back before we say that things are different? At what point does our assessment change? Does it change when we get to adolescent years, because if I think of the risky behaviors that I engaged in when I was a 14 to 16-year-old, I'm appalled and would not allow my children to do similar sorts of activities when they're the same age.

DR. GLANTZ: Could you say what they were?

DR. LEEDER: Sorry?

DR. GLANTZ: Could you say what they were?

[Laughter.]

DR. LEEDER: What they were? Chances are, my kids are not watching this.

[Laughter.]

DR. LEEDER: If this isn't on Facebook, my kids aren't seeing it. But I mean those are the types of--I'm also trying to figure out not only what's the difference, but where is the line or the age at which we cross

over in, and it's different?

And, boy, oh, boy, I can't see entrusting those kinds of decisions to a study section if I'm on it. And what did Groucho Marx say, if people like me are members of that club?

CHAIRMAN BOTKIN: Dr. Towbin?

DR. TOWBIN: Well, I'm glad that somebody raised the issue of the 407 panels because I'm kind of curious. This is more of a question than anything. I'm kind of curious about the role that those can play in these kinds of conversations and discussions having had only the most limited experience with 407 panels, it really is like sending the lamb out to the wilderness, that by the time such a panel is configured and anything is being done, you might as well just stop your study. It's really the equivalent of being given a life sentence without chance of parole.

And so, because I don't think the idea behind a 407 panel is a bad idea; I just think that it breaks down in the implementation, and

whether that might be yet an additional sort of avenue that if it was not quite so cumbersome, not quite so user-unfriendly, not quite so protracted in experience, whether a 407 panel could be a sort of remedy for some of these things. It's a question. I really don't know.

DR. NELSON: Well, if this protocol had not been withdrawn, you would have been the 407 panel, just to point that out. And so, you have met the enemy, and it is you. So, there is a cumbersome to the process. But go back to the protocol that was withdrawn, if this group had decided with a more in depth review of the science that, in fact, this healthy control was unnecessary for this protocol, then I'm assuming that you all would have decided it should not proceed.

So, in other words, independent of the ethical question about whether administration of these products would be considered minimal risk in a population that doesn't have a disorder or condition. So, again, we didn't

have to do that because the protocol was not on the table; it was mainly for a discussion of these issues, but that's precisely the process that we would have been in if, in fact, the control group had not been withdrawn.

DR. TOWBIN: My other experience, I guess two other experiences with things that were headed to or got to a 407 panel was that the turnaround time was somewhere in excess of 18 to 24 months. This looks like it's shorter turnaround time.

DR. NELSON: We have to talk about your experience and the timing of that, but I think that is a long estimate relative to our current process. So, the process is faster.

DR. FOST: And much of it was at the local level.

CHAIRMAN BOTKIN: Leonard?

DR. GLANTZ: Yes, I think that if we're a 407 panel, just to go further, we could say that a control group was necessary, but it still can't proceed. That the fact that the

control group was scientifically necessary doesn't mean that it's appropriate to do the research, and that's the other possibility.

DR. NELSON: I realize there may be different views on this. I don't want to get us into a sort of vote on a non-vote. I just wanted to make the point that, in fact, if that protocol was on the table, A, this would have been the panel, and B, we would have structured the day much differently. Instead of the opportunity for this more free-ranging discussion around the kind of issues that we could potentially incorporate in guidance, it would have been very focused upon coming to a specific decision about could it be approved under either of the categories of subpart D or could it only proceed as a 407, as I like to say a 50.54, which is the FDA group. And there would have been specific votes.

So, it would have been structured very differently. The fact that it was taken off the table meant that we could have a more free-

ranging discussion of the issues.

DR. GLANTZ: Right, but I just wanted to make the point that the fact that scientifically a control group was required doesn't mean that it should succeed. There would be another discussion about that.

DR. NELSON: Absolutely. But if yes doesn't mean it would proceed, but, obviously, if it didn't have scientific merit, then that would stop it there, as well. That's my only point.

DR. TOWBIN: And I guess my point in raising the question was that I'm not sure this is a terrible process if we're addressing this fourth question related to problems with IRBs, I'm not sure that this is a bad partial answer, maybe not the whole answer for some of the people.

DR. NELSON: Let me just make one final comment. We are at the end of our time. One of the challenges of the 50.54/407 process is that at least as the regulations occur and

is structured, it's unclear if we could use a panel as a precedent. So, let's imagine that a protocol came today, it was decided upon, whatever that decision was, and then another one that was exactly the same came forward a year from now, as the current regulations are structured, it's not clear because we haven't had that legal question asked whether we could use the decision from a year before to advise the decision a year later. So, there are some issues. That's separate from whether IRBs would be informed and use it in their decision-making. But that's a separate question.

CHAIRMAN BOTKIN: All right. Let me see if I can summarize in just a couple of sentences where we've been today. And I'll take one minute to invite any corrections for where people may think that this doesn't sound right.

It seems to me there's been a broad recognition of the need for better information about drugs in kids, but also some broader

uncertainty about this particular mode of innovative research and when is it essential to garner information about kids that can't otherwise be acquired through different methodologies? And I think there was a clear interest in wanting to push alternatives, when feasible, rather than to tread into this new territory. So, additional work sounds like it needs to be done to be convincing about the importance of this mode of research.

I think our group was somewhat open to the notion of some of this research being a minor increase over minimal risk. Certainly with lots of caveats about required information, in particular, human subject information specifically in making that determination.

I don't think we ever came to any clear conclusion about the minimal risk, although I certainly sensed a broad hesitancy around the table to even determine that this was minimal risk. I don't think we quite

pushed the question about if you get into these really quite microdoses, whether that might qualify. So, part of the conception around question three then had to do with possibly opening the door. What do we do if we open the door to lots of drug studies with normal, healthy children? I don't think this group was quite ready to open that door. So, some of the questions around exploitation that emerged from that possibility may be less acute right now.

In terms of question four, I think a number of creative suggestions. Should the field begin to move into this particular domain, then national consortia as a possibility, and we certainly see many more problems with investigator-initiated protocols than we do with the ones coming out of national consortia. Consent by non-investigators, additional FDA oversight for compliance with subpart D, more rigorous design characteristics as determined, perhaps, by expertise that would be drawn on by local IRB or perhaps move some

of these to a national stage with the central IRBs. And then the question of whether the 407 panel can be sufficiently flexible to pick up on some of these issues that don't clearly fit within the current established criteria.

Thoughts on that brief summary? Other key issues that people think should be emphasized?

Yes, Steven?

DR. JOFFE: Only to add to your point about consent by non-investigators. I just wanted to endorse the related point, which is consent not by a clinician responsible for treating that patient. So, the recruitment happens in a clinical arena.

DR. TOWBIN: I think it's quite a good summary. Just to add in some settings, there are people who oversee the consent process so that the person who knows the protocol best is the one who's explaining it, but a neutral party is there to kind of provide an ombudsman-like function. I have a little hesitancy about

people who don't know the protocol providing the consent. And so, I think that that can swing both ways.

CHAIRMAN BOTKIN: Good. Well taken. Well, my thanks to the group for a terrific conversation, and, Skip?

DR. NELSON: Yes, again, I would like to thank everyone for coming. I think it's been a fascinating conversation, and, hopefully, we'll have more in the future that cover some of these topics. Thank you again.

(Whereupon, at 3:05 p.m., the meeting was adjourned.)