DEPARTMENT OF HEALTH AND HUMAN SERVICES

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CENTER FOR DRUG EVALUATION AND RESEARCH

DRUG SAFETY AND RISK MANAGEMENT ADVISORY COMMITTEE (DSaRM)

Volume I

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Holiday Inn Gaithersburg
Two Montgomery Village Avenue
Gaithersburg, Maryland

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Robert Temple, M.D.
Andy Mosholder, M.D.
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C O N T E N T S

P R O C E E D I N G S

Call to Order

DR. GROSS: I guess we should begin. Good morning, everyone. Thank you all for coming. It should be an interesting two days. I would like Victoria to read the conflict of interest statement first.

Conflict of Interest Statement

DR. FERRETTI-ACETO: Good morning. The following announcement addresses the issue of conflict of interest with regard to this meeting and is made a part of the record to preclude even the appearance of such at this meeting. Based on the submitted agenda for the meeting and all financial interests reported by the committee participants, it has been determined that all interests in firms regulated by the Center for Drug Evaluation and Research present no potential for an appearance of conflict of interest at this meeting with the following exceptions, in accordance with 18 USC 208(b)(3):

Dr. Thomas Fleming has been granted a

waiver for his membership on two unrelated data safety and monitoring committees for one of the affected firms. He receives fees of less than $10,001 per year for each activity.

Dr. Steven Nissen has been granted a waiver for his consulting for an affected firm on an unrelated matter. He receives less than $10,001 per year, which is donated to charity.

Dr. Henri Manasse has been granted a waiver under 21 USC 355(n)(4), an amendment of Section 505 of the Food and Drug Administration Modernization Act, for ownership of stock worth less than $15,001. Because this stock interests fall below the de minimis exemption allowed under 5 CFR 2640.202(a)(2), a waiver under 18 USC 208 is not required.

Dr. Terry Davis has been granted a waiver for his ownership of stock in two affected firms. The stock values are between $5,001 to $25,000 and $25,001 to $50,000. In addition, Dr. Davis has been granted a waiver under 21 USC 355(n)(4), an amendment of Section 505 of the Food and Drug

Administration Modernization Act, for ownership of stock worth less than $15,001. Because this stock interests fall below the de minimis exemption allowed under 5 CFR 1640.202(a)(2), a waiver under 18 USC 208 is not required.

A copy of these waiver statements may be obtained by submitting a written a request to the agency's Freedom of Information Office, Room 12A-30 of the Parklawn Building.

We would also like to disclose that due to conflicts, Dr. Elizabeth Andrews is only permitted to give a presentation to the committee and to answer questions directly related to her presentation. She is recused from participating in any other segment of today's meeting.

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

With respect to FDA's invited industry

representative, we would like to disclose that Dr. Annette Stemhagen is participating in this meeting as a non-voting industry representative, acting on behalf of regulated industry. Dr. Stemhagen's role on this committee is to represent industry interests in general, and not any one particular company. Dr. Stemhagen is employed by United BioSource Corporation.

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

DR. GROSS: I would like to go around the table, for those of you who don't have 20/20 vision and can't read the labels in front of each person. I am going to start with Dr. Gerald Dal Pan, if everyone around the table and on the Drug Safety and Risk Management Advisory Committee could introduce themselves and just tell us where you are from.

DR. DAL PAN: Gerald Dal Pan, Office of

Drug Safety, FDA.

DR. IYASU: I am Solomon Iyasu. I am the Acting Deputy Director for Pediatric Drug Development, FDA.

DR. LAUGHREN: Tom Laughren, Director of the Division of Psychiatry Products at FDA.

DR. MOSHOLDER: Andy Mosholder, FDA, Division of Drug Risk Evaluation.

DR. LEVIN: Arthur Levin, Center for Medical Consumers and the consumer representative on the Drug Safety and Risk Management Advisory Committee.

DR. CRAWFORD: Stephanie Crawford, Associate Professor, University of Illinois at Chicago College of Pharmacy.

DR. FLEMING: Thomas Fleming, Department of Biostatistics, University of Washington.

DR. DAVIS: Terry Davis, Department of Medicine and Pediatrics, LSU Health Sciences Center, Shreveport, Louisiana.

DR. RAPPLEY: Marsha Rappley, Developmental and Behavioral Pediatrics, College of

Human Medicine, Michigan State.

DR. MOORE: John Moore, Professor of Pediatric Cardiology, UCLA.

DR. FERRETTI-ACETO: Victoria Ferretti, executive secretary for the committee.

DR. GROSS: I am Peter Gross, Chair, Department of Medicine at Hackensack University Medical Center, in New Jersey.

DR. GOMEZ-FEIN: Eleanor Gomez-Fein, clinical pharmacist, Jackson Memorial Hospital, Miami.

DR. MANASSE: Henri Manasse, with the American Society of Health-System Pharmacists.

MS. DOKKEN: I am Deborah Dokken. I am a member of the FDA's pediatric advisory committee as a family patient representative, and was asked to attend this meeting.

DR. NISSEN: I am Steve Nissen. I am a cardiologist at the Cleveland Clinic, and a former member of the cardiorenal panel of the FDA.

DR. GARDNER: Jacqueline Gardner, Department of Pharmacy, University of Washington,

in Seattle.

DR. FURBERG: Curt Furberg, Department of Public Health Sciences, Wake Forest University.

MS. SHAPIRO: Robyn Shapiro, Professor and Director of the Bioethics Center at the Medical College of Wisconsin.

DR. HENNESSY: Good morning. I am Sean Hennessy from the Center for Clinical Epidemiology and Biostatistics at the University of Pennsylvania School of Medicine.

DR. D'AGOSTINO: Ralph D'Agostino, statistician from Boston University and Director of the Statistical Analysis of the Framingham study.

DR. STEMHAGEN: I am Annette Stemhagen. I am an epidemiologist, United BioSource Corporation, and I am the industry representative to the committee.

DR. GROSS: Thank you all very much. We shall proceed with the opening remarks from Dr. Gerald Dal Pan, Director, Office of Drug Safety.

Opening Remarks

DR. DAL PAN: Good morning. I am Gerald

Dal Pan, the Director of the Office of Drug Safety, FDA Center for Drug Evaluation and Research. I want to take this opportunity to thank everyone for coming and joining us here for this morning's meeting with the Drug Safety and Risk Management Advisory Committee.

We are going to talk about a number of things over the next two days. Today's meeting will focus on research approaches that could be used to study whether drugs approved for attention deficit hyperactivity disorder, or ADHD as it is commonly referred to, increase the risk of adverse cardiovascular outcomes.

Many of you were here at the May, 2005 meeting when we spoke about the strengths and limitations of our passive surveillance system, the system through which we receive individual case reports of adverse events that occur in people taking medications. We spoke about the strengths and limitations of that system and we noted that it is very difficult with such a system to ascertain causality when an event has a high frequency in the

background population.

So, we discussed other kinds of approaches that use more epidemiologic approaches to ascertain causality or relationships between drugs and adverse events. We talked about case-control studies, cohort studies and using different kinds of databases to answer these kinds of questions. So, the topic we are going to discuss today illustrates the challenges and difficulties of how best to assess the relationship of adverse cardiovascular outcomes with drugs used to treat ADHD. You will hear more about that from our speakers this morning.

In the afternoon then we will ask the committee to discuss the feasibility of various epidemiologic approaches to explore this safety signal, and to address important methodological considerations.

Tomorrow's meeting will shift gears and will discuss things that have happened in the past year in drug safety. I will give an update on the Office of Drug Safety initiatives and activities.

Dr. Susan Cummins will give an overview of the newly established drug safety oversight board. Dr. Sharon Hertz, of the Office of New Drugs, will discuss FDA's activities related to nonsteroidal anti-inflammatory drugs that have occurred since the advisory committee met in February, 2005 to discuss that topic. Finally, Dr. Jill Lindstrom will introduce a discussion on the risk management program for isotretonoin, another topic that was discussed by this committee in the past.

The following FDA staff are joining me at the table today--they have introduced themselves already, Dr. Solomon Iyasu, Dr. Tom Laughren, and Dr. Andy Mosholder. So once again, thank you all for coming today. I look forward to our discussion.

DR. GROSS: Dr. Andrew Mosholder will now talk about overview of ADHD and its pharmacotherapy.

Overview of Attention Deficit Hyperactivity Disorder (ADHD) and its Pharmacotherapy

DR. MOSHOLDER: Good morning, everyone.

[Slide]

What I have been asked to do to set the stage for today's discussion is to provide an overview of attention deficit hyperactivity disorder, or ADHD as we are calling it, and also the drugs that are currently used to treat it.

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So, I will be covering several topics, first an overview of the diagnosis and clinical characteristics of the disorder and the current treatment, with an emphasis on the pharmacotherapy that we will be discussing today. I will present some recent data from the Centers for Disease Control and Prevention on the prevalence of ADHD and its treatment, and also some data on ADHD prescription drug use from the Verispan database.

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Turning first to discussion of ADHD, let me review for you briefly the diagnostic criteria, and these are from the American Psychiatric Association Diagnostic and Statistical Manual, fourth edition, which is known in shorthand as

DSM-IV. In your briefing packages, the article from the MMWR includes a summary of these criteria.

But basically, it requires symptoms of inattention and/or symptoms of hyperactivity and impulsivity, and there have to be at least 6 in one of the categories or it could be both categories. The duration has to be at least 6 months so this is a chronic disorder. Onset must be before age 7, and there should be impairment in more than one setting, typically school and home for children, social, academic or occupational impairment and the symptoms should not be accounted for by another mental disorder such as psychosis, mood disorder, anxiety, and so forth. There are subtypes that are recognized. If there is predominantly inattention, that is the inattentive subtype. On the other hand, there could be predominantly these types of symptoms and that is hyperactive-impulsive subtype. But the most common subtype is to have both types of symptoms together.

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What is the differential diagnosis?

Again, this is from DSM-IV: Age-appropriate activity, especially younger children, as everyone knows, can be quite active and that has to be distinguished from a true disorder. Cognitive impairment can produce some symptoms of hyperactivity. Children in disorganized and chaotic environments can display these types of behavior without actually having ADHD. It is possible to have oppositional behavior without ADHD, and other psychiatric disorders, as I have already mentioned and, finally, there are some drugs which have adverse reactions in children that can produce hyperactive type behavior.

[Slide]

ADHD has a number of common psychiatric comorbidities, and this is from DSM-IV: oppositional defiant disorder and conduct disorder in children together with ADHD, those three are referred to as disruptive behavior disorders. Mood disorders are common; anxiety disorders; tics and learning disorders.

[Slide]

There is a male preponderance and the ratios are estimated 4:1 up to 9:1 for males to females. I will show you some data, from the CDC survey that speaks to this, in a few minutes. It is a highly prevalent disorder. The estimates range from 3-5 percent in school age children--that is DSM-IV. A more recent review by Biederman and Faraone put it at 8-12 percent.

The etiology is unknown. Environmental, genetic, developmental and familial factors are all thought to play a role. The diagnosis is clinical. There are no pathognomonic physical or laboratory findings, and there is no psychological testing that can make the diagnosis for certain. So, it is based on the clinical characteristics. It is also important to remember that the diagnosis can be fulfilled with different levels of severity as long as a sufficient number of criteria are met. So, it allows for a range of severity within that diagnosis.

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We want to talk a little bit about adult

ADHD. Historically, the diagnostic criteria were developed for children, although DSM-IV does specify ADHD in partial remission which can be applied to adults who still have some symptoms but not enough to meet the full criteria for the disorder any longer. Adult ADHD in recent years has been increasingly recognized and treated, and there are now two drug products approved for the indication, which I will mention in a minute. In terms of persistence into adulthood, there is one recent retrospective study which estimated that 36 percent of children diagnosed with ADHD would have persistence into adults in this age range, in their survey.

[Slide]

Now, if we are going to talk about potential risks of drug treatment, it is also important for perspective to talk about some of the morbidities associated with the disorder itself, although it is not known to what extent the drug treatment might ameliorate these. Be that as it may, ADHD is associated with academic, familial and

occupational impairment as per the diagnostic criteria; also, delinquent and antisocial behaviors. There is an association with motor vehicle accidents. They have been found to be more frequent among drivers with ADHD compared to age-matched controls. There is some evidence, at least in driving simulator experiments, that methylphenidate can improve driving performance in patients with ADHD. ADHD in children is also associated with higher frequency of injuries of various types.

[Slide]

Continuing with morbidities, substance abuse is another comorbid condition which often will be found in adults who have had the disorder. There is some sort of mixed evidence that might be mitigated by pharmacotherapy but both alcohol and illicit drug use are increased in individuals with the diagnosis and also tobacco use. So, tobacco use and drug use--if we are thinking about potential epidemiologic type studies, those could be important confounders for cardiovascular

outcomes of course.

To illustrate, in one long-term prospective study tobacco and cocaine dependence were roughly twice as frequent among young adults with ADHD compared to the control group. There is also some evidence that stimulants themselves stimulate smoking behaviors, at least in the laboratory. So, those are important things to keep in mind as we think about studies of cardiovascular outcomes.

[Slide]

How is ADHD treated? Well, there is pharmacotherapy, which I will go into in more detail, but in addition to that there are behavioral, psychosocial and educational interventions which are also important. These are recommended by various groups, including the American Academy of Pediatrics, the American Academy of Child and Adolescent Psychiatry and also the current product labeling for these drugs. However, in a couple of recent long-term studies the efficacy of behavioral treatments above and

beyond that of the medication was somewhat difficult to demonstrate.

Turning now to the drugs that are used for ADHD, the biggest group are the stimulants and these are sympathomimetic compounds. I have listed them here: Methylphenidate, Ritalin being the oldest brand of that. There is also the d-isomer, dexmethylphenidate, which is Focalin; amphetamine, which is Adderall and Adderall XR; and there is also the d-isomer of amphetamine, dextroamphetamine, marketed as Dexedrine and its generics. Pemoline is a stimulant that is no longer marketed because of its association with liver toxicity. Finally, methamphetamine is marketed as Desoxyn for ADHD but it is used very little. A newer compound is atomoxetine, or Strattera, which is a selective norepinephrine reuptake inhibitor so that is not a classic stimulant. I should add that throughout the rest of the morning we will be referring to these by their generic names, but for reference this shows the brand names.

[Slide]

There is another newer compound under review for ADHD, which is modafinil, marketed as Provigil. It is a stimulant. It is not a sympathomimetic. Then there are drugs that are used off-label for ADHD. I have listed some of them here: tricyclic antidepressants, bupropion and alpha-2 agonists such as clonidine. In the case of tricyclic antidepressants and clonidine, which is sometimes combined with methylphenidate, in the '90s there had been some case reports of sudden pediatric death with both of those. So, there are some safety concerns there too, plus the well-known toxicity of tricyclics. So, those are not used to the extent that the other compounds are.

[Slide]

Focusing more on the stimulants, they have been used for decades. The principal compounds in use currently, as I mentioned, are amphetamines, such as Adderall. You should know that Adderall is a mixture of 25 percent l-isomer and 75 percent d. Then, there is, of course, the pure d-isomer

marketed, methylphenidate and also its d-isomer, and those are the principal stimulants.

These are available in extended release formulations which have become increasingly popular in recent years. They permit once a day dosing so that the child doesn't have to take a second dose while at school. Briefly, some of the adverse effects associated with these drugs--they are all drugs of abuse and are scheduled under C-II--are tics, cardiovascular events, as we will be discussing, central nervous system effects and also perhaps some growth retardation. Adderall XR is approved for the adult indication.

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Looking at the other compounds, atomoxetine, as I mentioned, is a norepinephrine reuptake inhibitor. Its best known adverse effects are hepatotoxicity and suicidal events. It does have an increase in pulse and blood pressure and also effects on growth. It is, unlike the stimulants, not a scheduled drug. It too is approved for adult ADHD.

Finally, modafinil is a different type of stimulant, marketed for excessive sleepiness associated with various sleep disorders. It is currently under review for ADHD. It too may have some cardiovascular effects and it is not a scheduled drug.

[Slide]

This is just a brief digression into a little organic chemistry. These are the structures of the drugs we have been talking about and, just for sort of comparison some related compounds that are known to have cardiovascular effects. Here is amphetamine. You will see what is referred to as the sympathomimetic nucleus which is phenylethylamine, the phenyl group. Then there are the two carbons and the amine group.

This is methamphetamine. Methylphenidate at first glance looks different but if you look, you see there is the same backbone with a ring enclosing it. I think you can also see that it is clear that atomoxetine and modafinil are rather different in their chemical structures.

Down here, at the bottom, are some compounds that have been associated with cardiovascular effects. Phenylpropanolamine was found to be associated with hemorrhagic stroke, and I think you can see the similarity to amphetamine. Aminorex was a European weight-loss product which was found to be associated with pulmonary hypertension and was removed from the market. Again, you see it has the sympathomimetic backbone there. Ephedrine is the main active ingredient in Ephedra, the supplement which has been the subject of concern regarding cardiovascular outcomes. I think you can see the similarities to these drugs. Finally, fenfluramine, which is sometimes referred to as a halogenated amphetamine, is, of course, associated with cardiovascular disease and pulmonary hypertension.

[Slide]

I want to shift gears now and talk about this recent survey from the CDC. It is the National Survey of Children's Health. It was a telephone survey conducted in 2003 to early 2004.

It involved around 100,000 subjects in this age range, 4-17. The parents or guardians in the household were asked to respond to questions about ADHD and its treatment for the children in the home. The sample was such that it allowed for statistical projections at both the state and national level.

[Slide]

Let's look at some of the results. This is a very rich slide in terms of the data presented so I will walk you through it. First of all, males are shown over here, on the left, and females on the right. Down at the bottom is the percentage of the respondents, going in this direction and in the other direction for females. Then, on the vertical axis is the age range. Now, the outside bars are the percentage of children who have ever had a diagnosis of ADHD within each household surveyed. Then, the inner bars are the percentage of children in the household who are currently receiving a medication for ADHD.

You can see several things here. First of

all, there is clearly a male preponderance compared to females. Secondly, you will see that the frequency of the diagnosis, lifetime diagnosis, tends to increase up to about age 10 and then it sort of levels off. So, one interpretation would be that few cases are diagnosed after these ages, 10-11.

You also notice that medication use for ADHD tends to peak around ages 9-12 in both genders and then it tends to drop off some. Relevant to contemplating studies, one thing this would mean is that it should be possible to identify individuals with the diagnosis but who are not receiving medication as a possible comparison group to individuals who are receiving medication.

[Slide]

Going further with some of the results here, this is a map by state of the percentage of children who have ever been diagnosed with ADHD in the survey. You see that the range here is from 6 percent up to around 10 percent. You see that there is some regional variation, sort of a

concentration in the southeast and less prevalence in the west.

[Slide]

This is a display of the current medication use for ADHD for the survey respondents. Again you see regional differences. The prevalence here ranges from around 2 percent to about 6.5 percent. You see again that there is sort of a concentration here in the southeast and relatively less prevalent use in the west. It is not clear why there are these types of regional differences but that was their finding.

[Slide]

The conclusions are that, first, there is a high prevalence of the diagnosis and medication use in children and adolescents in the U.S. The estimate is that 2.5 million children aged 4-17 currently were receiving a medication for ADHD at the time of the survey. That translates to 4.3 percent of all children in the age group. There is a clear preponderance of males over females. There are regional variations in both diagnosis and

medication treatment. Medication use appears to peak around ages 9-12, with around 9 percent of boys aged 12 and almost 4 percent of girls aged 11 receiving medication for ADHD. Of course, the limitation of this survey data is that it is dependent upon parental recall.

[Slide]

Moving on, we want to look at some current data on patterns of drug use for ADHD in the U.S. This comes from Verispan Vector One national database, or VONA. This data source collects data on prescription activity from retail pharmacies from multiple sources. It includes data on prescriber speciality, patient age and gender. Data are available for over 1.8 billion prescriptions per year for around 150 million patients. So, you see that it is a pretty broad sample. The limitations are that it does not provide data on indication or on the duration of treatment. It simply counts the prescriptions.

[Slide]

Here are the drugs that were selected as

relevant to treatment of ADHD. This line is the total over a 5-year period. You can see that over the past 5 years there has been a steady increase in prescribing of these drugs. Looking by individual compounds, you see that methylphenidate is the most frequently prescribed, followed by amphetamine. This is atomoxetine and some other compounds that are prescribed much less frequently.

[Slide]

This is essentially the same display but by quarter, going up to last summer. What this shows is that there is some seasonal variation in the use of these drugs. As people have probably guessed, these dips here represent the summer months. Interestingly, atomoxetine does not show that type of seasonal variation. Then if you look here, the total is almost exactly 9,000 per quarter--I am sorry, I should point out these are in thousands so that is 9 million per quarter or 3 million per month.

[Slide]

If we look at the active ingredients--this

is data from the most recent 6-month period that we have available--you will see that methylphenidate has the largest share with 41 percent; this is the combination represented by Adderall, 35 percent; atomoxetine, 15 percent; and some other smaller categories for the other compounds. Modafinil, of course, is marketed for other indications.

[Slide]

Let's see what we can learn by looking at this by age groups. This displays the total dispensing in thousands for adults, this is adults, and for under 18. You see again that there is seasonal variation for the pediatric use not seen in the adult use. Use is increasing in both groups. This covers little more than a 3-year period, by the way. You see that the adult use has increased pretty substantially during that period, proportionally more than the increase in the pediatric use.

[Slide]

If we look at it by more specific age groups, this is the pattern we see. There is a

very small amount of use under age 5; 18 percent of the total use is age 5-9; almost 48 percent in the 10-19 age group; just over 20 percent in young adults. One thing I want to draw your attention to is that the 15 and over age group now represents 10 percent of the use of these compounds. So, if we want to think about cardiovascular vulnerabilities, obviously this would be the age group that would have those risk factors.

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To conclude the overview from the Verispan data, there has been increasing use of the drugs by both adults and children. The increase for adults in roughly 3 years was about 90 percent so that is increasing even faster than in the pediatric age group. That translates to roughly 1 million prescriptions each month for adults for these drugs and about 2 million per month for children. If you remember the CDC estimate of 2.5 million children currently being medicated, if you figure one prescription per month per child, that is in the same ballpark as the CDC survey.

Methylphenidate is the most frequently prescribed, followed by amphetamine and atomoxetine and, as I mentioned, 10 percent of the use is now by adults over age 50.

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I will stop there. I want to acknowledge Susanna Visser and Ruth Perou from the Centers for Disease Control for allowing me to share the data from their survey, and also from our own Office of Drug Safety, Carol Pamer for assistance with the Verispan drug use data. I will stop there.

DR. GROSS: Thank you very much, Dr. Mosholder, a very interesting presentation.

DR. NISSEN: Would it be possible to ask questions about the presentation, or do you want to wait until later?

DR. GROSS: Go ahead.

DR. NISSEN: You know, one of the things you didn't cover were the heart rate, blood pressure effects, that is, the physiological effects of the agents. Have they been studied? Are there differences between the agents? What do

we know about those effects on blood pressure and heart rate for example?

DR. MOSHOLDER: Well, Dr. Gelperin, who is going to speak next, has some information on that but, briefly, amphetamine and methylphenidate are, of course, sympathomimetic type compounds. Atomoxetine has a different mechanism of action but it still can be associated with some increases in pulse and blood pressure. Those are described in the label. I should have added that the labeling for all of these compounds is included in your briefing packages. I don't have the specific findings in mind but they are in the label. In the case of modafinil, there was a finding that use of antihypertensives during the clinical trials was more frequent than on placebo, which suggests that there are some cardiovascular effects there as well.

DR. NISSEN: I guess I was more interested in understanding--

DR. GROSS: Why don't we hold until Dr. Gelperin?

DR. NISSEN: Okay.

DR. GROSS: But I thank you, Dr. Nissen, for the segway to Dr. Gelperin's talk on studying cardiovascular risk with drug treatments of ADHD.

Studying Cardiovascular Risk with Drug Treatments of ADHD

DR. GELPERIN: Good morning.

[Slide]

This morning I am going to try to tell you a little bit about why the FDA is worried about these issues, telling you a little bit about the MedWatch reports we have received. We will talk about sudden death in children and adults. We will talk about some calculated reporting rates and background incidence, and also some non-fatal cardiovascular events. I am going to try to tell you about what we see when we look at the MedWatch cases in the FDA safety database and, yet, not feel that we can determine the level of risk involved just from these MedWatch cases alone. What are the challenges? What are the study options? We are going to seek advice from the committee about

approaches and elements of optimal study design such as selection of optimal endpoints, power considerations, what age groups to target, selection of a comparison group, and identification of important confounders or risk factors.

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Of course, biological plausibility is one of the points to consider, adrenergic agonists, and there is a known effect of sympathomimetic drugs on blood pressure, which is described in some of the labeling; precautions against use in patients with known risk factors such as coronary artery disease or structural cardiac abnormalities are in some of the labels and, as Dr. Mosholder had mentioned, some structurally similar compounds have shown safety issues related to their pharmacologic effects in some patients.

[Slide]

Drug treatment of ADHD is increasing in all age groups, as you just heard, and also drug treatment for ADHD can now potentially be life-long.

[Slide]

Dr. Nissen had asked about effects on blood pressure and heart rate. This slide has a lot of information on it but it basically gives some references showing that in studies which looked at it mean change from baseline in blood pressure and heart rate have been documented for amphetamine, methylphenidate and for atomoxetine in clinical trials with adults.

[Slide]

Why are we concerned? The seventh report of the Joint National Committee on Prevention, Detection, Evaluation and Treatment of High Blood Pressure has pointed out that in adults usual blood pressure is strongly and directly related to vascular and overall mortality; that data from observational studies involving more than one million individuals have indicated that death for ischemic heart disease and stroke increases progressively and linearly from blood pressure levels as low as 115 mmHg systolic and 75 mmHg diastolic upward. These increased risks are

observed in adults above the age of 40.

[Slide]

Very few long-term studies have been done in adults with ADHD. We found one long-term by Dr. Biederman and his group looking at cardiovascular effects in adults. After a 4-week, double-blind, placebo-controlled trial, a long-term open-label extension study was undertaken with 223 otherwise healthy adults with ADHD. The mean age in the study was around 40 years and they were 59 percent male. These patients received up to 24 months of amphetamine mixed salts extended release formulations, 20-60 mg a day. The resting blood pressure and heart rate were measured at baseline, weekly and then monthly during long-term treatment. Twelve-lead electrocardiograms were obtained at baseline, weekly, then at 3- and 6-month intervals up to 14 months.

The study showed that mean changes from baseline in diastolic blood pressure, systolic blood pressure, pulse at QTc interval were statistically significantly increased, although the

investigators did not consider this to be clinically significant. The mean changes in systolic blood pressure were on the order of 2.3 mmHg; diastolic blood pressure 1.3 mmHg and no subject had a corrected QTc greater than 480 milliseconds. However, the majority of the subjects did not complete the 24-month study and 7 subjects discontinued from study due to cardiovascular adverse effects, 5 with hypertension and 2 with tachycardia.

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In children there have been two studies using ambulatory blood pressure monitoring methods. Both were small studies but they both showed statistically significant differences in the diastolic blood pressure during active treatment compared with placebo, as well as total heart rate.

The study by Samuels and colleagues studied 13 subjects with a mean age of 12.5 years who underwent ambulatory blood pressure monitoring both on stimulant therapy and placebo, using a placebo-controlled, double-blind, randomized

crossover design. These patients continued on their usual stimulant medications which included methylphenidate, amphetamine or dextroamphetamine at the usual doses.

After a 3-day run-in, followed by a 24-hour monitoring period subjects crossed over to the alternate therapy for repeated ambulatory blood pressure monitoring. The subjects demonstrated elevations in most hemodynamic parameters derived from ambulatory blood pressure monitoring during the active treatment period. Total diastolic blood pressure was 69.7 mmHg versus 65.8 mmHg. That was statistically significant. The total heart rate was also significantly higher during active treatment. The rate pressure product, which is the product of systolic blood pressure by heart rate, which is an index of myocardial oxygen demand, was higher during active treatment and this was statistically significant.

[Slide]

Very few long-term studies have been done in children. They are listed here. In general

these studies have yielded little information on cardiovascular risk.

[Slide]

MedWatch cases, which are spontaneous reports that are received by the FDA and are compiled in the adverse event reporting system safety database, have been reviewed for various reasons over the past few years and a question has been raised about whether there is a potential cardiovascular signal for some of these ADHD drugs. The non-fatal cardiovascular reports have included conditions including syncope, chest pain, myocardial infarction, stroke and arrhythmias. However, as is typical of spontaneous reports, often these cases are not well documented so there are limitations in our ability to understand their clinical relevance.

There have also been reports in children and adults of sudden death. These have been analyzed. You received in your background package a 5-year analysis. The calculated reporting rates do not exceed the background rates, however we do

not know the extent of under-reporting.

[Slide]

There was a pediatric advisory committee last June at which the one-year post exclusivity review of adverse events which occurred during the year 2004 for methylphenidate products was conducted, and there were two possible safety concerns that were discussed, one of which was cardiovascular adverse events.

At that meeting, the reported cardiovascular events included a few cases of hypertension, syncope, chest pain, prolonged QTc, arrhythmias and tachycardia. The advisory committee agreed with the FDA at that time that it is not yet possible to determine whether these events, especially the more serious ones, are associated causally with these treatments. The committee felt that the FDA should pursue additional means to characterize the cardiovascular risks for all drug products approved for ADHD. Potential options under consideration include population-based pharmacoepidemiologic studies,

long-term safety trials and other targeted cardiovascular risk studies.

[Slide]

So, I would like to try to explain some of the limitations of calculating what are called reporting rates from spontaneous reports. First, under-reporting. It is just not known how much it is. Does the FDA get 10 percent of all the cases? Does it get one percent of all the cases? Nobody knows and it is probably different for different scenarios. So, the numerator is just not reliable for many reasons. Also, the denominator, which is the drug use data, is really an estimate based on national projections.

So, we cannot calculate incidence from reporting rates and a comparison of reporting rates to background incidence or between drugs is really only a rough estimate. Of course, there is always confounding to take into account, which is are there other drugs on board; are there pre-existing conditions or risk factors.

[Slide]

I am going to tell you about some searches that were conducted of the FDA's adverse event reporting system safety database. You have some of this information in your background package. I know it is rather lengthy and it probably looks pretty inscrutable. I am also going to present some updated information that was developed by Dr. Lourdes Villalba.

We looked at cases of sudden death and the definition that we used is one that has been used by the World Health Organization, which is death occurred immediately or within 24 hours of an acute collapse. In all of these analyses we excluded cases in which death was caused by multi-drug overdose, or if drug abuse was reported, or if death was clearly most likely due to another cause.

[Slide]

To give you a perspective on pediatric sudden death, I would refer you to a review article from the New England Journal which really was quite comprehensive, and it is in the background package. It includes data on 469 sudden deaths from 9

studies of large populations. The rate of sudden death in these populations ranged from 1.3 to 8.5 per 100,000 patient-years, with males consistently outnumbering females. In two-thirds of the cases a specific cardiac cause was identified. Extrapolation of these data suggests that each year several thousand Americans under the age of 20 years die suddenly from cardiovascular disorders. For ages 1 through 30 years the most common cardiac causes of sudden death include myocarditis, hypertrophic cardiomyopathy, coronary artery disease, congenital coronary artery anomalies, conduction system abnormalities, mitral valve prolapse and aortic dissection.

[Slide]

This is the comprehensive reporting rate analysis that was completed by Dr. Lourdes Villalba in the reviewing division. Let me try to explain what you are looking at. Using these generic names we are basically referring to all branded or generic products and all formulations of drugs which contain methylphenidate, drugs which contain

amphetamine and/or dextroamphetamine and atomoxetine.

For all age groups we obtained information about the total number of perspectives dispensed during the time period from 1992 through 2004 from IMS. These are the total prescriptions that were dispensed during that time. I should note that atomoxetine is a drug that was approved by the FDA in November of 2002 so there are only two years of drug use data for this drug, whereas methylphenidate and amphetamine and dextroamphetamine, of course, are very old drugs.

Using NDTI estimates of the breakdown of use by adult and pediatric age groups correction factors were applied so person-year calculations were done for each of these products for the pediatric age group in person-years. I can tell you a little bit more about that calculation if you would like to know how that is done. This column includes the number of cases--that in Dr. Villalba's review, were considered to be unconfounded in the sense that there was no obvious

drug abuse or the other factors that I mentioned--of pediatric sudden death. Here are the reporting rates.

So, if you think in terms of the background incidence that I was telling you about in the previous slide, you can see that these numbers are below that background incidence. However, you can imagine that we could apply correction factors to adjust for under-reporting that could put us up in the same range. So, there is really a question that we would like to have answered.

[Slide]

You often hear about the limitations of spontaneous reports but I would like to tell you about one of these cases that I think illustrated for us the potential hazard of a child, with a previously undiagnosed structural cardiac abnormality, starting on a relatively high dose of a stimulant. This pediatrician reported to us that a 13 year old male collapsed while working at his computer and he died suddenly after taking a single

dose of amphetamine mixed salts, 20 mg, for the treatment of ADHD. He had been seen by a physician for a physical exam the previous day, with complaints of school problems and was diagnosed with ADHD.

At the exam his blood pressure and his heart rate were normal. His weight was 118 lbs. He was reportedly active in sports. He took a single 20 mg dose of the immediate release formulation at 10:30 in the morning. He complained of tiredness about midday, and he collapsed at his computer in later afternoon. A pulse was present when emergency personnel arrived but he was pulseless at the hospital.

An autopsy showed idiopathic hypertrophic subaortic stenosis and an enlarged heart which was said to be "filling his complete chest." The number of tablets was correct in the remaining drug supply and no concomitant medications were reported. The reporting physician considered that the cause of death was cardiomegaly and arrhythmia.

[Slide]

Now on to adult sudden deaths, you can see by looking at this slide that once you hit the age of 35 sudden death is actually not a rare occurrence. For men, by the age of 45 the rate is around 1/1,000 and for women by the time of 55 the rate is about 1/1,000, and it increases steadily with each advancing decade.

[Slide]

So, as you might expect, the calculating reporting rates for sudden death in adults were really substantially below background rates and, as has been mentioned previously, for events that are not rare in the general population spontaneous reports are usually not a good way to understand what is happening.

[Slide]

I am going to tell you a little bit about non-fatal cardiovascular adverse events from the 5-year review that you have in your background package. As I had mentioned, these were identified as a potential signal in some FDA reviews. Although they are different from sudden death, they

may be more readily studied in claims databases since they can be identified by ICD-9 codes, and sudden deaths can be problematic to identify in claims data.

[Slide]

So, for pediatric cases with methylphenidate--and these are serious events only, and serious is a regulatory definition which means that the report was classified as requiring hospital admission or being life-threatening. So, non-serious cardiovascular cases are not included in this listing. For methylphenidate in the 5-year time period there were 8 reports. The mean age was 11.5 years; 5 males, 3 females. And, these cases included syncope, loss of consciousness--these are the reporter terms--dyspnea, palpitations or arrhythmia in 6 cases, 1 abnormal heart biopsy, 1 non-fatal cardiac arrest, 1 stroke and 1 case of QT prolongation.

[Slide]

In adults on methylphenidate there were 11 reports during that time period, which included 2

cases of syncope, 3 cases of hypertension--and, again, these required hospital admission--3 cases of chest pain, 1 heart failure, 3 myocardial infarction, 2 arrhythmia, 1 case of mitral valve prolapse and 1 case of stroke.

[Slide]

During that time period for amphetamine in the pediatric age group there were 18 reports, 15 male, 3 female. There were 2 cases of syncope, 6 cases of hypertension, 4 dyspnea, 1 myocardial infarction, 5 arrhythmia, 1 left ventricular hypertrophy, 1 thromboembolic stroke and 1 subarachnoid hemorrhage.

[Slide]

In the adult age group there were 17 reports with amphetamine; mean age of 42 years; 11 male, 6 female; 2 syncope, 3 hypertension, 4 chest pain, 3 dyspnea, 5 myocardial infarction, 6 arrhythmia, 3 cardiomyopathy, 3 stroke and 2 cardiac arrest. Again, as we had mentioned previously, many of these cases are very incomplete in their details and are really very hard to

interpret as to their clinical relevance.

[Slide]

For atomoxetine, which was only approved more recently, in November, 2002, there have also been similar reports received. These MedWatch reports have included cases of arrhythmia, syncope, cardiac arrest, myocardial infarction and stroke both in pediatric and adult patients, and these cases are currently under review.

[Slide]

So, there are many challenges at hand for our discussion today. As you could imagine, we are interested in not just acute but also chronic effects of these drugs. You can see the very different background rates for the different age groups for the events of interest. There is an unknown impact of confounders such as underlying diseases or abnormalities, and the clinical development programs for the newer and the older drugs would reflect different requirements at the time of initial approval.

[Slide]

Some of the study methods we might think about--a large simple trial is very attractive but would power and feasibility be barriers for useful study in this condition? Would there be ethical issues such as patient or parent acceptability of randomization? Then, of course, such a study would be hugely expensive and who would pay for this?

[Slide]

There are pharmacoepidemiologic approaches. I am going to tell you briefly about a case-control study that is under way looking at pediatric sudden death. In particular, we are going to seek your advice today about a large population-based epidemiologic study that the FDA has undertaken for research contracts and is at the feasibility stage.

[Slide]

The case-control study that I want to tell you about, the principal investigator is Dr. Madelyn Gould, at Columbia. The major aim of her study is to examine the relationship between sudden death in children and adolescents and the use of

tricyclics or concomitant methylphenidate and clonidine, which Dr. Mosholder had mentioned was an issue in the mid '90s that had come to attention in the published literature, although we don't see those drugs used as often today for ADHD.

So, the cases are pediatric sudden deaths during the period of 1985 through 1996 identified using state vital statistics data. The target number of cases is 400 sudden, unexplained deaths. The controls are children and adolescents killed in motor vehicle accidents, and the data are still being collected.

[Slide]

Dr. Gould has shared with us that a major difficulty in conducting a case-control study for pediatric sudden death is the identification of an appropriate control group and the availability, or unavailability, of comparable outcome measures.

She has also found that when looking at medical examiner data there can be much variability in the toxicology screens that are performed. Privacy issues can make it harder to obtain

relevant records, and there is difficulty getting a large enough study population to get enough power.

[Slide]

Dr. David Graham is going to tell you shortly about the feasibility study and some of the findings to date in terms of whether there could be enough power by combining the four FDA research contract awardees, which would yield 23 million covered lives.

[Slide]

Other things that perhaps the cardiologists in the room might want to comment are would echocardiography studies help us out here? Could we look at risk factors versus chronic effects looking at cardiomyopathy or valvulopathy? Should we follow a prospective cohort over time? Should someone do a prevalence study of users versus non-users?

[Slide]

Should we do a cardiovascular PK/PD study, including an assessment of heart rate, blood pressure and QTc during exercise? Do we want to

have a good collection of PK data for PK/PD correlation? And, there is an FDA guidance document that talks about such studies.

[Slide]

Should we be studying lower doses, characterize the lowest effective dose and the lowest effective dose producing the maximal therapeutic benefit? The dose-response relationship at lower doses may not be known and may have a safety advantage. And, is there a possibility that some of these adverse effects are occurring in poor metabolizers? Should we be looking at issues like that?

[Slide]

I would like to acknowledge my colleagues in the Office of Drug Safety and the Division of Psychiatric Products, especially Dr. Lourdes Villalba who worked on the comprehensive reporting rate analysis.

DR. GROSS: Thanks very much, Dr. Gelperin. The next speaker is Dr. David Graham who will talk about ADHD drugs and cardiovascular

outcomes, feasibility study results.

ADHD Drugs and Cardiovascular Outcomes:

Feasibility Study Results

DR. GRAHAM: Good morning.

[Slide]

This morning I would like to talk about a feasibility study that we have done in our epidemiology contracts program with the goal of seeing whether or not it seems practical and possible to address this issue by observational study means.

[Slide]

By way of background, the epidemiology contracts program replaces a cooperative agreement program which we previously had for about 15 years. Its purpose is to provide us with the capability of addressing safety issues in a population context and, at the same time, to be able to collaborate with outside, non-government experts that can sort of complement the in-house expertise that we have.

Currently, there are four awardees. Kate has already gone over who these sites are. You can

see the number of covered lives that each of these programs has. An important aspect of these databases is that they are related to health insurance provision. So, in each of these databases what is required, for the first three at least, is basically that you be employed and that you get the health insurance through your employment. The last database, the Medicaid databases, are those talking about people who satisfy income criteria for being below the poverty line so there isn't the same age censorship there. So, these first three databases are going to be relatively deficient in patients over the age of 65.

Another aspect to recognize is that the turnover in these databases can be quite high. At one year the turnover ranges from about 8 percent to 30 percent, and over 5 years from 25-80 percent. So, this has implications for the capacity to study long-term effects on use of a drug. Then, at the bottom of the slide you can see what the funding is for each of these programs, and by research

standards this is really a very small sum.

[Slide]

I will describe a little bit what the feasibility study is that we did with the goal of trying to see whether this could be studied in depth. For each of the drugs of interest we established inception cohorts that included all ages of patients exposed to the drugs. An inception cohort is someone who, by our definition, during the study period had not received a prior treatment with an ADHD drug for at least 6 months before starting treatment during the study period which, as you can see, covered a 7-year period for three of the databases and a 4.5-year period for one of the databases.

These were the drugs of interest, the ones that Andy and Kate talked about, and we were interested primarily in two age groups, children and adolescents as one age group and then adults as the second age group of use, but ending at 64 years of age because there isn't much use above that in these databases.

The outcomes of interest were the cardiovascular outcomes, some of which have been talked about previously. In addition to unexplained death and myocardial infarction, we have stroke, arrhythmia, hypertension and pulmonary hypertension.

[Slide]

This slide shows the base population of these four databases combined. What you can see is that overall we have about 23 million covered lives, of which 7 million were in the age of children and adolescents. The number of person-years of observation is about 45 million person-years in the children and adolescents group and 95 million in the adult group. This is quite a large base population.

[Slide]

Within that base population we identified these inception cohorts for the three drugs that we are interested in. This slide breaks down by age category and drug the number of people who entered the inception cohorts, the number of people who

were newly treated with each of these ADHD drugs. You can see, for example, that for amphetamine we had 191,000 children under the age of 20 and a little over 200,000 children on methylphenidate and about 80,000 on atomoxetine, for a total of nearly 500,000 children treated with these drugs over the study period we examined. Likewise for adults, about 174,000.

[Slide]

This slide looks at the use that each of these patients had of the drug and sums it up in person-time so we can see the cumulative exposure of drugs that we have to work with. What we can see is that we have nearly 400,000 person-years of exposure to these ADHD drugs in children and about 100,000 in the adult age group. You can also see the breakdown by drug and age group. I should mention--well, it is on the slide, but those were in thousands, those numbers.

[Slide]

This slide is just to show basically what the sex ratio is with the drugs, the male to female

use. We can see, as was shown in previous slides by Andy, that in our population as well the use in children is predominantly in males, the ratio being about 3:1, and in the adult group it is pretty much even, male to female.

We don't have a good explanation for why that is. Two thoughts have come to mind. One is that the indications that are being treated with adults may not be all ADHD so other conditions being treated could lead to other indications and that could equalize the gender ratio. The other that came to mind was that women are more likely to seek medical care than men and so people who see a physician are more likely to get prescriptions and maybe what we are seeing is a reflection of that. In any event, the reality is that there is equal gender distribution of use in the adults.

[Slide]

The next two slides show the duration of use, persistency of use over time in children and adults for each of the drugs that we are interested in from our inception cohorts. What I would like

to point out is that for methylphenidate and for amphetamine we see very parallel curves, with a median duration of use of about 8 months.

The other thing to note is that there is a very steep decline during the first 2 or 3 months. What that suggests is that most people who are treated with these drugs, or at least a third of the people who are treated with these drugs only stay on them for a very brief period of time. Then also if we look at longer periods of time, say beyond 12 months, beyond 24 months, we have relatively few patients who remain on the drugs for that length of time. So, this has implications for our ability to study duration of use effects.

[Slide]

With adults we see a similar pattern of use. The median duration is a little bit shorter, about 6 months for amphetamine and methylphenidate. For atomoxetine the median duration of use is a little bit shorter. That is primarily due to, we think, the fact that the drug has been on the market for a relatively short period of time so the

effect of censorship of use, because of the end of our study period, has a greater effect there.

[Slide]

I would now like to talk a little bit about the cardiovascular outcomes of interest for which we were able to obtain background rate information: sudden unexplained death, acute myocardial infarction and stroke of all types. For other events that we are interested in, such as arrhythmia, there are really no good statistics that one can point at to come up with background rates, especially in children, so we haven't presented that here.

As Kate presented in her talk, the background rate in children and adolescents for unexplained death is somewhere between 1 and 9 per 100,000 per year. In adults, in the 20-64 age group, it ends up being about 45 per 100,000 per year and over the age of 65 it goes up to about 700 per 100,000 per year.

With acute myocardial infarction--these rates were estimated from data that the American

Heart Association has published combined with census data, and we come up with an incidence rate between 10 and 20 per 100,000 per year but there is a lot of uncertainty about the accuracy and reliability of that rate. In adults below the age of 65 it is about 200 per 100,000, or about 2 per 1,000 per year. Over the age of 65 the rates exponentially increase.

Finally for stroke in children and adolescents, it is a relatively uncommon occurrence once you get beyond the period of infancy. During the age between 0-1 the rate of stroke in children is very high but after that it becomes fairly low and throughout adolescence is about 3 per 100,000 per year. This rate has been reproduced in two or three very large population-based survey studies. In adults below the age of 65 the rate is about 150 per 100,000 per year so it is very close in incidence to what we have for myocardial infarction.

[Slide]

So, we are dealing with relatively rare

events in children and slightly more common events in adults. This slide describes, within the inception cohorts that I have described to you already, what the number of events was that we identified after they entered the inception cohort based on primary discharge diagnoses from the hospital. So, these outcomes represent hospitalized outcomes; they are not outpatient diagnoses. It was the number one diagnosis, the discharge diagnosis. These numbers would be larger if we included secondary diagnoses, and it is not uncommon for people to have more than one diagnosis. Because we are dealing with primary hospital discharge diagnoses, these groups are independent so there is no double counting of individuals.

What I would like to point out now are just a couple of things. One, that we had 17 identified myocardial infarctions in children and about 700 in the adults that we are interested in studying. There were 14 cardiac arrests within this inception cohort, at least they have an ICD-9

code and a primary discharge diagnosis of cardiac arrest. So, these were deaths in hospital. And, 76 in adults. For stroke we had nearly 50 in children and about 400 in adults. For arrhythmia we had a fairly substantial number and this was somewhat surprising. The codes that we used to identify arrhythmias included both supraventricular as well as ventricular arrhythmias, so it is atrial and ventricular, but I would point out that these are hospitalized arrhythmias so for many of the more benign arrhythmias--tachycardia, paroxysmal ventricular tachycardia--I mean atrial tachycardia, things that wouldn't normally be hospitalized, would not be included in this code.

These are counts based on discharge diagnoses. They do not represent validated diagnoses. So, we don't know, for example, are all these strokes actually strokes. We do know from the literature that a primary discharge diagnosis of myocardial infarction has a very high positive predictive value in claims data. So, these probably, by and large, represent acute MIs.

Stroke also has a fairly high positive predictive value. But for others, other ischemic heart disease, cardiac arrest, arrhythmia, is really a very mixed bag and validation of the medical claims by going back to primary medical records would be an essential component of any in-depth study.

Finally hypertension--these represent hospitalized cases of hypertension where the primary diagnosis is hypertension. You have to recognize that with typical hypertension you don't hospitalize people for that. Hypertension in children isn't all that common. So, although the numbers seem relatively small, this is an area of concern.

(Slide.)

Finally, within the inception cohort, this slide shows the number of deaths that occur within each inception cohort from all causes. So it is not only these causes that we are interested in but other causes. This would include deaths from trauma, deaths from cancer, deaths from infectious diseases.

These deaths can occur anytime after cohort entry. That is important to realize because, as shown on the persistency slide, people don't remain on these drugs for extremely long periods of time. You might be in a health plan for years but only have been on ADHD drugs for eight months. So that means that there is a lot of unexposed time in the record of each child, each adult, that we followed.

So we don't know where in the history these deaths occurred. That would be something else that could be done in an in-depth study.

These deaths represent in-hospital deaths only for two sites. One site didn't report any deaths because they didn't think to look for them. One site was able to give us out-of-hospital sudden deaths as well as in-hospital deaths plus they had linkage of death certificates to the databases.

It turns out that at one other site, we had a total of two sites, that had this linkage and so we were able to identify from death certificates sudden cardiac deaths. Sudden cardiac death has

been validated in one of the databases. That is a Tennessee Medicaid database. For identifying out-of-hospital deaths with other databases that we talked about, the national death index would have to be searched.

A couple of things to realize here are that hospital turnover, and we talked about the high turnover rates in these databases, you will have people disappearing from the database. They are in the inception cohort and they disappear. Then the question is, will they disappear because their health insurance has changed or because they died. So there would be many, many names or Social Security numbers that will have to be searched in the National Death Index to identify those who were true deaths as opposed to the majority of whom are alive but in some other healthcare setting. It would also take a fair amount of time and probably a fair amount of money.

Finally, because of the fact that we are only deaths hospital deaths, and we didn't capture out-of-hospital deaths and from one site we didn't

capture any deaths, these numbers here are substantially underestimated of what actually occurred in these inception cohorts.

[Slide]

Cardiovascular disease in children is relatively uncommon and when it occurs it is usually associated with other identifiable causes. So, we went to the literature to identify from the literature what were viewed as being commonly associated conditions with cardiovascular disease in children. That is what this long list of conditions is. Next to it are the number of patients within our inception cohort who had at least one diagnosis for these conditions during the time of their being in the inception cohort.

Unfortunately, we don't have these numbers stratified by age group, except for two of the plans. What I can say from that is that within the inception cohort, when you look at children from these two plans but not from our largest plans, the conditions that sort of stuck out, if you will, as being prevalent to a relatively high degree were

congenital heart disease and conduction system abnormalities. So, we don't know how those correlate with people who had events and that would be something that would be needed to be looked at in an in-depth study, but it suggests that there are potential confounders or risk factors, if you will, that we would need to identify.

I mean, think about structural cardiac abnormalities, if it is not symptomatic it is not going to be diagnosed and most structural cardiac abnormalities aren't diagnosed. IHSS, idiopathic hypertrophic subaortic stenosis, isn't usually diagnosed until you are, like, on death's doorstep or after you have died. So, the idea of being able to identify these people antemortem, before they die or before you treat them with the drug is something to keep in mind because probably there are many people who are being treated who have these underlying conditions which are not known to them or to their physicians. So, they are potentially at higher risk.

[Slide]

Well, no talk about a study feasibility would be complete without a discussion of power. So, the next five slides or so talk about estimates of power, that is, the strength of our study to find a particular outcome event identified, if it is present.

What I have tried to do is break it up into sort of myocardial infarction in children, stroke in children and then MI or stroke in adults because the rates for those are pretty similar in the adults.

What we have here, just to sort of explain, is that I show three different relative risk levels, from a risk ratio of 2 up to a risk ratio of 5, and the exposure cohorts in thousands of person-years. So, if you go back to one of the previous slides where I showed the amount of person-time that we have for each of the drugs by age group or overall, you could identify what is theoretically our study power.

For example, with methylphenidate we had about 220,000 person-years of exposure in children.

So, we go over here to about 220,000 and we have better than 80 percent power, theoretically at least, to detect a 2-fold increase in acute myocardial infarction in children. That is theoretical based on this background rate. If this background rate is inaccurate, and it may very well be, then these estimates would be inaccurate as well.

[Slide]

For stroke, because the background rates are substantially lower, the amount of power that we have is lower as well. So, if we use the same example, methylphenidate in 220,000 person-years of use, we go up and we see that to detect a relative risk of 2 we would only have maybe 20 or 30 percent power. It is only when we get up to somewhere between 3 and 5 that we have sufficient power to detect reliably a risk ratio. Again, that is based on this background rate.

[Slide]

Finally for adults, looking at myocardial infarction and stroke, we have less exposure but we

have higher background rates. So, for example, if we were to look at all-use combined in adults there were about 100,000 person-years of use, and we go up on the slide and we see that we have more than enough power theoretically to identify a 1.5-fold increase in myocardial infarction or stroke in adults if we combined all drugs together.

[Slide]

Another way to think about study power is can you cap the risk at a particular level. That could have implications because you may be willing to accept a certain level of risk but find another level of risk unacceptable. So, you can do a study that might not have enough power to nail down and say, oh, the risk is definitely a 2-fold increase or a 3-fold increase but you might still have enough power to say we can be 95 percent or 80 percent certain that the risk isn't greater than some level. Depending on what that level is, you might make a judgment that the benefits exceed the risks. You might also say, well, no, that is too high a potential risk to justify whatever the

benefits are. So, this is another way of looking at study power.

If we were to assume that the relative risk was 1, which is to say these drugs do not increase cardiovascular risk at all, we go back to our example of methylphenidate and what this says is that we have enough power to cap the risk at about 3. What that would mean is that if there were no association between methylphenidate and myocardial infarction, none whatsoever, the confidence interval that we would have would exclude a relative risk of 3. So, basically what we could say is that the relative risk is no greater than 3.

[Slide]

This is for stroke again, but here we would be talking about a much higher relative risk. The cap on the risk would be as high as a relative risk of 10 which probably wouldn't provide much assurance to anyone because a 10-fold increase in stroke risk would be extraordinarily high.

[Slide]

This shows the same in adults.

[Slide]

Now, in this slide what I have attempted to do is combine the information from the slide I showed earlier that showed person-time by age group and by drug with the power calculations that I have shown. What is filled in each of the cells is what is the relative risk that we have--the risk ratio that we have at least 80 percent power to detect based on the background rates that we are working with.

What you can see from this example is that for the individual drugs we can detect a risk ratio of between 4 and 5 for amphetamine or methylphenidate and 10 for atomoxetine, and that is because the use of atomoxetine is so low. But if we were to combine all these drugs together we would have pretty good power to detect a relative risk of 3. In adults we have much better power to detect a relative risk of 2 and, when we get all the drugs combined, less than 2. For myocardial infarction you can see sort of what the numbers

work out to be again, and also for stroke.

[Slide]

Now, there are some additional considerations to power that need to be discussed at this point. The way I have estimated study power here is based on background rates from the literature and the person-time of exposure that we have in our inception cohorts. When you do that, as is shown in this slide, I have the age groups and the two conditions for which we have background rates, what the background rate was from the literature and what the number of person-years is for all groups combined, and what the number of expected events would be if this background rate was applied and then what the number are that have been reported in our system, recognizing that with secondary diagnoses these are probably somewhat under-estimated.

Before going into depth in the slide, there is one other way to look at study power. It uses the same principles of background rates and amount of size that you have in the study, but it

is looking at power based on the number of events that you need to have in order to demonstrate a particular relative risk. This is an approach that is used quite frequently in randomized clinical trials where a clinical trial would be designed to capture X number of events. So, you will say we will do this study until we have accumulated 100 myocardial infarctions because you have done these power calculations that say with 100 myocardial infarctions we can detect a relative risk of 2 or 1.5.

So, if we look from that perspective, the number of events and what we have--although the relative risks that we showed previously for myocardial infarction for all drugs combined was about 3 based on the background rates that we have shown, with 17 events we really only have 80 percent power to detect a relative risk of 5 or 6. What that suggests is that either we have under-ascertained myocardial infarction or the background rate that we are dealing with is higher than what the real background rate is. I don't

know what the answer to that is but I just want to point out to the committee that there is another way of looking at power.

For stroke, on the other hand, we have far more events than we would have expected, and if you approach power by the number of events that we have, we have substantially more power based on the number of events than what is shown in the power curves that I presented.

I have circled here the myocardial infarction numbers just to highlight the fact that we have this discrepancy and it could relate to ascertainment of cases or to the background rate. Also, we have substantial numbers of cerebrovascular accident reports so that would appear to be something that can be studied.

However, we shouldn't jump to conclusions. The reporters out there shouldn't say, "oh, looking at this we have shown that ADHD drugs increase the risk of stroke in children" because we haven't shown that. The reasons why you shouldn't jump to those conclusions are that these are based on

primary diagnoses only. There could be secondary diagnoses. Well, that would argue to make things higher but these haven't been validated. Furthermore, they may not have occurred during periods of exposure. So, those are important factors because if you have somebody who is treated with an ADHD drug for 6 months, stopped it and then a year later has a stroke--well, I can't attribute that stroke very easily to their previous ADHD treatment. So, that is important to keep in mind so, reporters, please don't jump to conclusions; you will create a panic before it is necessary.

[Slide]

Finally, please understand that these are preliminary results. We have had crude definitions of exposure and outcome. The outcomes haven't been validated. These represented outcomes after entry into the inception cohort. Their relation to current exposure isn't known. The power calculations are crude and there is uncertainty about background rates.

[Slide]

Nonetheless, I think, as Andy pointed out in his talk and as Kate pointed out in hers, there is a pharmacologic basis, a biologic plausibility to be concerned about cardiovascular risk with these drugs. The public health importance arises from the very high prevalence of use in children and a growing prevalence in adults. From the public health perspective, this use in adults, although it may seem to be relatively small in terms of the overall use of the drug, its importance may be as great, or greater, in terms of the number of lives that are impacted because the background rates are much higher in adults.

So, if I increase the risk of death by a factor of 2 in adults and the background rate is 50 per 100,000 per year and now it is 100, I have created another 50 deaths per 100,000. For children, if I am increasing it from 3 to 6 or for 100,000 kids, I have increased the deaths by a number of 3. So, it is not to diminish the importance in children, but it is to say that the fact that the use in adults doesn't seem to be so

tremendous, it still could be a very important public health question.

Sudden unexplained death is I think what initially got us very concerned about this. After looking at these feasibility data, arrhythmias have also jumped out at us as something that is important. But with respect to sudden unexplained death, it is a very difficult outcome to study and I think Sean Hennessy, on the committee, is involved in a study right now where he is looking at this. I have done studies in the past looking at sudden death, and Wayne Ray, in Tennessee, has done quite a number of studies.

What Wayne has shown is that it is possible to study these outcomes. So, with Tennessee Medicaid and with the Kaiser Research Institute, Kaiser Permanente in California, both of these places have death certificate linkage. So, that would facilitate the identification of sudden deaths. With Tennessee we have the ability to go back about 20 years. So, in terms of the amount of person-time that we could accrue, it is quite

substantial. Wayne has informed us that they have about 150 or 200 sudden deaths over this time period in children, which would suggest the possibility of addressing this question for at least methylphenidate and amphetamine.

For a feasibility study we see that we have substantial person-time of exposure. The outcomes would require validation. Our power appears to be sufficient to address a number of the outcomes of interest.

And, the number of arrhythmia hospitalizations really struck us as surprising, and we don't know how many of these are atrial versus ventricular; how many of those represent aberrant pathways in conduction system abnormalities that could be congenital in nature. But the fact is that there is a substantial number of them and with the pharmacology of these drugs, certainly, it wouldn't be unexpected. Realize that arrhythmia is believed to be the primary pathway or mechanism for sudden unexplained cardiac death. So, you put these things together and I think it

sort of increases I guess our desire to go forward with a study.

[Slide]

This last slide just shows for each of the contract sites the principal investigator for each of those sites, and from the FDA the principal people who have been working on this, but the actual study team is much larger. Thank you very much.

DR. GROSS: Thank you, David. We are going to stick to the schedule so we have a break now, and it will be longer than is on the schedule. We will reconvene at 10:15. Thank you.

[Brief recess]

DR. GROSS: The next speaker is Elizabeth Andrews who will talk about the challenges of studying cardiovascular outcomes in ADHD.

Challenges of Studying Cardiovascular Outcomes in ADHD

DR. ANDREWS: Thanks very much.

[Slide]

I was asked to speak to you about

methodologic issues relating to the measurement of three cardiovascular outcomes--myocardial infarction, stroke and sudden death in ADHD--primarily focusing attention on the use of large electronic databases. I hope that this overview will provide some frame of reference for the subsequent discussion that you will be having.

[Slide]

As an epidemiologist, as I look at the questions that emerge from the briefing book and from this morning's presentations, I have five basic questions: What is the absolute risk of myocardial infarction, stroke and sudden death in users of ADHD medications? Is that risk higher than the risk in the general population? Is the risk of these outcomes higher in users of ADHD drugs compared with people who have ADHD who don't use these drugs? Then, do these risks, if they exist, differ across the different drugs for ADHD? Given the complexity of the issue and the difficulty of studying these outcomes, I am left with another question which was mentioned in Dr.

Graham's talk, what is the upper limit of a potential increased risk associated with these products, within the limits of study feasibility?

I think all of these are interesting and important questions but I think first it is important to understand what are the consequences of the answers, and I think we should start with the ultimate goal.

[Slide]

I was going to phrase this as a question but I turned it into a declaratory statement--we should be measuring the risk difference, not the relative risk. It is important that we look at measures that have an impact at the population level and that are understood. As we have heard this morning, if we have a baseline risk of 1/100,000, a 10-fold increase in risk sounds really scary. That might equate to a risk difference of 9/100,000 or 9 additional cases of an event, which may still sound scary but is easier to understand in the population context.

So, two policy questions: What are the

added risks, if any, and what risks would have public health or policy significance, given the benefits of treatment, an aspect that we really haven't discussed very much this morning? Then, what level of increased risk would be acceptable to patients and their families? And, I haven't really heard any talk about that question but I think it is an important one.

[Slide]

So, we can consider what an ideal study would look like to answer some of these questions. First of all, we would select from a database or recruit into a large cohort individuals who have ADHD. Then we would separate those into those who have received treatment with ADHD medications and those who did not and then we would have a general population comparison.

In our ideal study we would be able to know exactly when each of these individuals took their first dose of an ADHD treatment and when they took their last dose, and exactly what dose they took and how they complied with the drug, and we

would understand that for each course of therapy and when they switched. We would be able to identify 100 percent of the outcomes of interest with absolute certainty and be able to characterize those events by severity and other characteristics.

We would be able to measure all risk factors. We would be able to look back into prior medical history and understand the risk factors for cardiovascular outcome, including cardiac abnormalities that may not have been identified, and we would be able to capture information on all confounders, including substance abuse which, as we have heard, have been important in a number of the cases that have been reported to the FDA.

Our follow-up would be absolutely complete. We would follow all of these patients over multiple years to be able to observe risk over time, drug switching over time, and our analysis would give us an absolutely unbiased comparison of the differences across all of the groups of interest. We would have sufficient precision to be able to rule out relatively small increases in

risk.

[Slide]

Now, we all have to face the fact that we will not be able to conduct the ideal study and we will be forced, because of the rarity of the events, to utilize to some extent large electronic administrative databases. So, I would like to drill down into each of these categories of sort of protocol development, not that a protocol should be developed by committee but I think this helps to frame the issues as we consider the feasibility of studies.

First of all, let's talk about subject selection. Shall we limit a study only to those individuals who are treated with ADHD medications? Those are easy to identify in a claims database.

Will we restrict the study to those who have documented diagnosis of ADHD? That may be more difficult because a prior diagnosis may or may not exist in a claims record, especially one that goes for extended periods of time.

We will obviously want some type of

comparison group not treated with ADHD medications and, as we have heard, for many reasons it is very important to look in pediatrics and also in adults and we may want to consider whether to limit the age distributions at the lower ends and the higher ends or include all ages consistent with the utilization of these products and just stratify the results. Of course, as one were developing a protocol one would consider whether there were exclusions to be made a priori.

[Slide]

I think a real key question relates to how we look at exposure. Does it make sense to consider all drugs for ADHD in a single category? Ideally, we would like to be able to differentiate across individual drugs. That is probably not possible. Does it make sense to categorize the drugs into stimulants and all others?

How do we consider the other drugs that don't have specific indications for ADHD? I think we heard that tricyclic antidepressants, bupropion and other drugs are sometimes used in ADHD but they

are used more often for depression and other indications. Do we need to attempt to evaluate the utilization of those drugs in ADHD? I would initially say no, but if our study ultimately leads us into different treatment recommendations we might wish we had information on the cardiovascular events associated with those drugs in ADHD.

Then I would point out that we need to think about whether to include incident users or, as Dr. Graham mentioned inception cohorts, versus prevalent use. From what I could tell, we don't know a lot about the distribution of the risk of cardiovascular events according to duration of use. With many products the highest risk period is in the early days or weeks of treatment. However, in this particular case we may have a risk that could increase with cumulative exposure over time.

It would be very important, therefore, in any study that we choose to design to identify new users so that if we picked only individuals who were already using the product we might find that we had excluded individuals who had already been at

the highest risk and we were looking at people who were predominantly lower risk. So, we should select all new users and use as much data as we can to verify that there was no prior use, which is a tradeoff in database studies where we would like to have lots of follow-up time to evaluate events, but we also need to look at prior time to exclude risk factors and other exposures.

Well, shall we look at multiple medications for the same patients? We know that patients do switch from one treatment to the other and it seems that we would be smart to look at all periods of use for these products but being aware that maybe there is an issue with risk over time if patients are switching among the stimulants.

[Slide]

The outcomes of interest would be acute myocardial infarction, stroke and sudden death and they share certain features. The rates, as we have already heard are extremely rare in children and they are much more common in adults. The risk factors for these events also vary by age.

[Slide]

Let's look at myocardial infarction. Most cases result in a patient coming to medical attention so there would be a claim for service and we could identify most cases through administrative claims. Prior studies--and there has been a substantial amount of work done in this area--have demonstrated a very high positive predictive value in using claims algorithms to identify cases of myocardial infarction. Therefore, we would not be faced with the challenge of having to abstract medication records on every patient where there was a claims diagnosis of MI.

One of the limitations, however, in using a claims database to look at myocardial infarction is that there would be some cases, particularly those that resulted in sudden death, that might not be seeking medical attention and, therefore, not be in the database. This would be an issue if the drugs were preferentially associated with an increased risk of sudden death as opposed to myocardial infarction that was not acutely fatal.

If that were the case we would, in a claims only database, miss that association.

[Slide]

The study of stroke is very similar to myocardial infarction in that most cases do result in medical attention. Cases can be identified through claims, and prior studies, using just hospital diagnosis in Medicare, have shown a fairly high positive predictive value that accuracy would probably increase with the inclusion of diagnostic procedures, as well as prescriptions following the hospitalization. Claims alone, however, will not be able to differentiate between ischemic and hemorrhagic stroke so some chart review might be needed, or the evaluation of claims for prescription of drugs to identify users of anticoagulants as a marker of ischemic stroke.

It would also be important to distinguish between new and repeat strokes. From the literature that I reviewed, over 20 percent of hospitalizations for stroke were actually repeat strokes, and I think the issue we would be

interested in here would be incident stroke unless one thought that these drugs might increase the risk of stroke in those who had prior strokes. And, again, cases not resulting in medical attention, acute deaths, would be missed in most claims databases.

[Slide]

So, I think stroke and MI are fairly straightforward to evaluate in electronic databases. Sudden death will be the most difficult. Most cases don't result in medical attention. If exposed cohorts are followed from electronic claims data there needs to be a link to vital records to be able to ascertain deaths and to obtain information from death certificates. Death certificates are not the best source of information on cause of death but when there has been an autopsy, then the cause of death will be recorded much more accurately and the death certificate will indicate whether or not an autopsy has been performed and they will be performed for most cases of sudden death in children. So, we can have

reasonable assurance, although it would be most useful to be able to evaluate the coroner's reports to understand the circumstances of death and try to understand whether these deaths were actually sudden cardiac deaths.

[Slide]

You have already seen one extensive list of risk factors for these events. This is a small list of risk factors but in designing these studies it would be important to do a thorough evaluation for each of the individual outcomes of the risk factors that are most important to those outcomes. Some of these outcomes will be readily available in claims databases, such as diabetes, epilepsy, treated hyperlipidemia. Prescription medications will be available in the databases.

Other potential risk factors will probably not be available in a claims database, specifically hypertension unless it is treated, cardiac abnormalities unless they have been diagnosed and are still in a current claim. Other factors that I think are important to these outcomes include race,

smoking, substance abuse and obesity which will not be available at all in claims databases and will not be reliably recorded in electronic medical records.

[Slide]

So, let's think about the study design. This diagram is a clear representation of the differences between a cohort study and a case-control study. What this represents is a source population in which the white circles are the exposed individuals and the black circles are the unexposed individuals who were followed over time until they developed the outcome of interest. Say we are looking at stroke, these would be the cases of stroke in unexposed and exposed and from this we can look at the rate of events by exposure level.

We get almost the identical result from a case-control study where we look at the cases which were exactly the same cases as in our cohort study, but what we do to understand the distribution of exposure is to take a random sample of the source

population and then, when we do a similar analysis, we will compare the exposure rate between cases and controls and should come up with the same result.

[Slide]

In a cohort study we will identify new users of the drug. We will include only those who have in their prior 6-12 months no exposure to other ADHD drugs and we will follow them forward for the development of the outcomes of interest or until the end of follow-up. For those patients who switch drugs, in our protocol development and analysis plan we will create operational definitions of risk period that are consistent with use and prescribing patterns. In a claims database it is important to understand that we will know the date that a prescription was filled and we can assume the duration of treatment to be roughly 30 days. Most prescriptions are for a 30-day period. But we don't know much about compliance and we don't know what happens when they start another drug. We will have to make some assumptions about how to deal with gaps and overlaps in prescription

records. Then, obviously, we will follow the individuals without ADHD treatment similarly.

[Slide]

In a case-control study there is a very similar process. We will identify cases and non-cases and then look at their prior exposure to ADHD drugs, controlling for everything else, and we have the same issue in creating operational definitions of exposure periods relevant to the outcomes.

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In terms of the data collection strategy, it is clear some of the data, as we have said before, will be available in electronic claims. These include age; sex; some of the demographics; exposures to the ADHD medications; the outcomes, at least in MI and stroke. We will develop algorithms to identify these based on inpatient and outpatient and prescription drug records. We will be able to identify many potential confounders through their medical claims and we will look at patients longitudinally looking at observation time prior to

and after their initial exposure.

[Slide]

But for the data that are not available from the electronic claims, if we think that information is critically important to obtain we will have to look at some supplemental data collection strategy. You have already heard that there is the ability, at least with some data sources, to link those patients who have been lost to follow-up and who have no continuing medication claims for service with vital records to ascertain death and perhaps even obtain copies of coroner reports to understand cause of death and circumstance of death and whether there have been prior unrecognized cardiac abnormalities.

Medical record abstraction has been one of the mantras of drug safety epidemiologists--you know, never do a study of an outcome without being able to validate claims. However, in the case of stroke, MI or myocardial infarction we may not actually need to abstract records on all of those events to validate the events. However, if it is

important to distinguish between ischemic and hemorrhagic stroke we may need to pull some records for those that are not clearly identifiable based on claims.

[Slide]

Then, for the information that is not in any medical encounter records, like race, body mass index, smoking, perhaps over-the-counter aspirin use and substance abuse, one would have to obtain that information directly from patients or families. That could be done through some type of survey of patients with ADHD. This is a picture of someone participating in a survey online. It could be done through telephone, mail or in-person interviews.

[Slide]

This is not a simple issue and it is not a single study. The study questions really sort themselves by the three different outcomes, or perhaps four if arrhythmias are to be included, and they sort themselves by pediatrics and adults. Risks for these outcomes and risk factors differ

between pediatric and adult populations. For example, cardiac abnormalities will play a larger role in these outcomes in pediatrics than in adults. Cigarette smoking will be more important in adults. Then, the risk factors may differ across the outcomes. For example, epilepsy is a risk factor for sudden death but probably not a risk factor for MI or stroke so six different sets of analyses will be needed in order to address these questions.

[Slide]

The analysis plan should be fairly straightforward to measure the incidence of each event as the number of cases over person-time of relevant exposure comparing the incidence of events by exposure category, whether that is all ADHD drugs or stimulants versus others versus the general population. In ideal circumstances, we would like to stratify on age, gender and other important covariates. In adults, because the outcomes are more common, we might be able to model the incidence ratios for ADHD drugs versus the

general population using some multivariable modeling techniques where we can control for measured confounders. Then, in the ideal study we would compare drugs or at least drug categories.

[Slide]

For these confounders that cannot be measured from an electronic database we can, as I mentioned before, conduct a survey to understand the prevalence of these confounders in the ADHD population. Then, we can use the information from that survey and from the medical literature to make external adjustments to control for confounders and estimate the amount of bias that might have resulted. So, in this case we will obtain the prevalence data from a survey. We will obtain prevalence data on the confounders in the general population from the literature or from other national surveys. Then, from the literature we can look at the size of the association between these confounders and outcomes--there is a substantial literature on things like smoking and MI--and then use that information and apply it to our study to

adjust, as we would do any external adjustment, and then conduct sensitivity analyses to understand the extent of the bias that could have resulted from failure to identify these unmeasured confounders.

[Slide]

You have already seen some power curves but I think the point can't be overstated that the size of these studies will be driven by the outcome rates, but they will be restricted by the availability of data sources. These outcomes are extremely rare in pediatrics, with rates less than 2/100,000 so, at best, our study may be able to establish an upper bound of a potential increase in risk.

[Slide]

This is a different sample size curve which assumes a baseline risk of 3/100,000 over a follow-up period of 3 years which might be the best you can do from some claims databases. We assume that the expected relative risk is 1. So, what can we rule out? This is the probability that the upper limit of the confidence interval will be less

than 3. If you extended this curve to get up to an 80 percent probability that the confidence limit will be less than 3 would require approximately 450,000 patients in each of the 2 exposure groups assuming a 1:1 ratio of exposure to non-exposure--so, a very ambitious sample size.

[Slide]

The outcomes are much more common in adults so we may actually be able to compare risks between drugs and look at some of the risk factors, and this is a much more manageable study.

[Slide]

This is the same type of curve for an event that occurs 3/1,000 over a 3-year period. Here we are looking at the probability that the upper confidence limit will be less than 2, and we will be able to reach that point with 90 percent probability with about 16,000 individuals in each exposure group, and I think that is very achievable from the data that we saw from the feasibility study.

I wanted to point out, back to the issue

of children, that I am assuming that we are looking at these large claims databases but there are other sources of information and we have to consider the national children's study that is under development, sponsored by a number of federal organizations. That study will attempt to enroll 100,000 infants, actually enrolled prior to birth, and follow them to the age of 21. That will allow an enormous amount of very precise measurement on an annual or semi-annual basis of various exposures. However, for the issue that we are looking at I think even that large study will not be sufficient for our purposes.

[Slide]

If we go back to our ideal study design we see that there are quite a few differences between the ideal and what we are likely to be able to achieve. Three problems that I think are troublesome but perhaps not insurmountable are that sudden death will not be completely captured probably in any scenario, although it looks like, from the Medicaid databases at least in Tennessee

and I believe it was Washington State that we will have a better chance than in other places. Race information will not be measured directly and substance abuse information, even under the best circumstances or confidential surveys, will not be complete.

[Slide]

So, a few final points on study design: The data collection and analyses need to be tailored to each of the 3 different outcomes. Analyses will differ between children and adults because risk factors are different and rates of events are different. No single database will be sufficient so we will be faced with the need to pool information across multiple studies. Large medical databases, such as claims and electronic medical records, are absolutely essential to this kind of research. However, they are limited to medical encounters and associated data so they will not be sufficient for everything, but they can be supplemented through linkage, for example, through vital records data and may be supplemented by

patient-based surveys and also chart extraction.

[Slide]

So, as we think about the possible relationship between ADHD medications and their benefits and their potential increased risk of cardiovascular events over the general population or patients not treated for ADHD, it seems that policy decision is key. It would be ideal if we could establish the threshold and understand what is the level of increased risk given the benefits that would dictate a change in prescribing behavior, compliance behavior and willingness of families and patients to assume the risk of a product to deal with the ADHD symptoms.

If we established that policy threshold, then our job would be much simpler in designing the research. Where the data are feasible to collect we could design a study that would address these levels of concern. If such a study is not feasible, then we could continue active surveillance in order to further reduce the uncertainty about potential increases in risk.

Thank you.

Questions and Answers

DR. GROSS: Thank you very much, Dr. Andrews. The floor is now open for discussion from the members at the table.

[Audio malfunction]

DR. NISSEN: I will try to speak up. I am pretty soft-spoken so it is hard. The question I want to get some answers on from any of the sponsors or anyone in the agency is we know that these drugs all increase blood pressure and heart rate. Let's for a moment make an assumption that those changes and physiological parameters are the explanation. The parameters are the main drivers around these sudden deaths, arrhythmias and stroke that we are worried about. So, clarity about the relative effects of these agents on those physiological parameters would be very useful. For example, do we know that the amphetamines are more likely to raise blood pressure and heart rate compared to, let's say, methylphenidate. You know, what do we know about the newer agents? This would

be very helpful because we can't study everything here but we have to have some prior information. The reason this question I think is very relevant for the committee is that we know that other agents in this class, like Ephedra and phenylpropanolamine and fenfluramine, and so on, have this effect. So, I would like to know have there been any comparative studies? Can anybody help us understand the physiological effects of these drugs?

DR. GROSS: Dr. Dal Pan, whom would you suggest?

DR. DAL PAN: I would ask Dr. Gelperin if her review of the literature identified any comparative studies. Then I would also like to ask Dr. Laughren if he is aware of any studies.

DR. GELPERIN: I would also like to put the same question to colleagues in Neuropharm., but what struck me in looking at the literature is that because for ADHD really the clinical trials are short and small typically, and efficacy is demonstrated fairly expeditiously, there is very

little long-term information. Also, cardiovascular measures--I am not aware of them being identified as an endpoint for careful assessment, such as, you know, a thorough QTc evaluation. Also, blood pressure, as I am sure Dr. Nissen knows, if it is only measured once you would tend, in a placebo-controlled clinical trial, to bias toward null effect because it is not a very precise measure. For instance, if you are developing drugs to treat hypertension you measure the blood pressure 3 times and you identify it as an endpoint of interest; it is not an incidental measure. But I think I would ask my colleagues to address that.

DR. LAUGHREN: I can comment briefly on the type of studies that we typically see in development programs for these products. They are generally of two types. We have what are called laboratory classroom studies which are usually small, brief in duration, crossover studies, and almost never have comparison drugs. It is usually the drug of interest versus placebo. Those are probably the best data we have looking at blood

pressure and heart rate, and even those are not ideal because that is not the primary purpose of those studies.

Then you get to the outpatient studies which are, you know, often 2, 3 to 4 weeks where, again, you rarely see an active comparator and it is not a requirement of law to compare these drugs in a development program so that is why we don't typically see those studies.

So, the bottom line is that we don't have very good head-to-head comparisons across drugs in this broad class that precisely measure changes in blood pressure and heart rate, not that I am aware of.

DR. GROSS: Just an editorial comment, if the requirement to do head-to-head comparisons is something not in the law, maybe the law ought to be changed because we need that for more than just these drugs in general. Yes?

DR. RAPPLEY: There are two studies from 2004 and 2005, open label, one, in 2005, an open-label extension of a randomized, controlled

trial. It had 568 patients and it looked at the cardiovascular parameters we have been discussing on long-acting dextroamphetamine and amphetamine products. The other did the same in a one-year open extension trial, with 432 patients with long-acting methylphenidate. So, while the same children weren't compared on these medications, it is quite a lot of information looking at both long-term dextroamphetamine--long term being one to two years, and methylphenidate.

DR. NISSEN: And the magnitude of those changes, if you could share that with us?

DR. RAPPLEY: Well, you know, maybe I will see if I can get copies of this and share that with you because I have not analyzed the difference myself.

DR. GROSS: Robyn?

MS. SHAPIRO: From my perspective, the discussion is lacking a big piece in that in order to do risk management we have to assess risks--and I appreciate the safety signal discussion--against benefit and I haven't heard nearly what I need to

hear about benefit. I think that with respect to this drug and this condition it is particularly important because we are treating a lot of children. So, if the benefit, for example, is to make life easier for the decision-makers, that being their parents, patriae obligation is that we have as the state, as the government, as the regulator, to figure out whether the risks are reasonable in terms of the benefits is a critical piece of this conversation and I haven't heard anything about it.

DR. GROSS: Dr. D'Agostino, you had a question?

DR. D'AGOSTINO: It is on a different topic; can I move to a different item? What I wanted to ask is a couple of questions from either David or Elizabeth in terms of the studies and the power issues. In trying to think of this afternoon, I am bothered by the sort of parameter of abuses. I was involved with the PPA studies and we talked about designing epi-type of studies and we ran into a lot of trouble with the new users

versus duration, and so forth, and I don't get a sense from the power calculations--there is just so much you can do and I want to congratulate the presenters for all the work they did do, but there is just so much you can do in terms of putting these together. But it seems to me the power calculations are all sort of driven on person-years. Even though you pay lip service to maybe new users versus long duration, and so forth, none of that seems to be clarified in the calculations. What if it really is new users? What if you really have to build up long use? I don't see those coming in and I don't know how to really evaluate some of the items in the power calculations that were given.

Another question--I will just rattle off my few questions and, hopefully, get some answers. Another is the risk factors by age. It seems to me like it is a different study in children than it is in adults. So, are these power calculations really for the six different possible studies or do you somehow or other think you can combine the data? I

am not sure you really can. I think you are looking for different things in the children than you are in the adults. I think we can do sort of traditional cardiovascular types of studies for the adults; I am not so sure with the children.

Then, the other idea is this case-control and taking a random sample. I have been involved in so many case-control studies where we have taken a random sample and we said those are going to be our controls, and they don't look anything like the cases in terms of risk factors, and should we control for them, and so forth? So, I am not sure that we have heard how one can really grapple with the control issue and getting good controls. I know we will go over and over this but if we could hear some discussion on that or some answers to my questions I would really appreciate it.

DR. GROSS: Dr. Graham, do you have some answers?

DR. GRAHAM: Well, maybe. Regarding the first question about new users versus prevalent users, in the data that we presented from our

feasibility study, those were all incident users so they are new users. Now, if you compare the two slides, one slide shows the actual number count of patients who are new users and then the adjacent slide is the person-years contributed by those new users in toto. So, if you look at the two slides I think there are maybe, like, 450,000. If you look at age 0-19, there are about 450,000 individuals treated with any of the three drugs that we are talking about, and you can see the number for each cell in the slide. In the next slide is the number of patient-years. So the 450,000 individuals contributed about 400,000 person-years of time on drug.

Now, observation time in that entire cohort is much larger than just the 400,000 person-years because there is time off drug, and we followed them from when they entered the inception cohort until they either left the database or the end of our observation period.

So, skipping your second question for the moment and getting to the third question on the

control groups, we didn't talk about that intentionally here because the idea was to pick your brains for grappling with that. That is always a difficult situation. All these studies rise or fall on the control group.

There are two thoughts that I have. One is that time on drug isn't forever. We see that people don't stay on these drugs for a long, long period of time. That tells us one thing, that we are probably not going to be able to look at the effects of chronic use very well. But for shorter-term use we probably can take a look at that, and we might be able to use the same patient's time off drug as a comparison, basically summing up person-time on drug, person-time off drug, and looking for the occurrence of events during those, because with distribution of events we don't know where those events fall with respect to use. So, in that design the comparator group would actually be unexposed time within the inception cohorts.

The second comparison group that comes to

mind is probably less satisfactory, and that is to take a population control that is not exposed to these drugs. The reason why I say that is because, as Elizabeth pointed out in her talk as well, it is virtually impossible to identify people with ADHD who aren't being treated. The diagnosis isn't uniformly used. It has not been validated. It probably has a lot of misclassification in it so the only way you know that somebody has it is if they are being treated with the drug.

Now, the second question--could you repeat your second question, the one in between?

DR. D'AGOSTINO: Yes, I think the potential studies of young--

DR. GRAHAM: Oh, yes, young and old--

DR. D'AGOSTINO: --would be different than in old.

DR. GRAHAM: Yes, there is no question that that will be the case. When we looked for the potential confounders, our oversight was that we didn't ask it to be stratified by age and outcome. I wish we had but we didn't so all we know is sort

of in very crude terms what we have. The idea would be that we would, of course, have to adjust for these in the in-depth study.

In terms of adults versus children, yes, the risk factors that we are interested in will be different. In terms of how we go about these two studies and whether they are feasible or not, in the power calculations that I gave, taking the slide that had sort of the matrix of age by drug and number of person-years in each of the cells and then combined sort of for each age group overall for the drugs, then going to the power curves--and the power curves that I showed had two for children, one based on a background rate for MI, another based on the background rate for CVA, and then for adults separately we used the background rate for adults to try to come up basically with power calculations that are tailored to the amount of person-time we have in those particular age groups and what the background rates were for those disorders in those age groups.

So, I think we tried to address the

question you have. You know, my own assessment is that we probably have sufficient power, I think, to answer shorter-term effects in adults. I think we probably have a lot of power to do that. I think in children we probably can cap the risk on stroke. I think that for MI we may not have adequate power to do it because either the background rates we have from the literature are wrong or we have under-ascertained those cases.

Then, there is this question of arrhythmia. Hospitalized arrhythmia in children, at least from conversations with pediatric colleagues within the agency, is not a terribly common occurrence. The fact that we have such a large number, may be that is by chance but we are not going to know unless we go and look at it. And, arrhythmia, of all the outcomes we are talking about, is probably the one that is most biologically plausible in terms of the effect of catecholamine stimulation or cardiac conduction and that could lead to sudden death, or catecholamine stimulation could lead to vasospasm and stroke or

myocardial infarction or to hypertension and cerebral hemorrhage.

So, I have tried to answer your questions as best I can. You can determine if it was satisfactory or not.

DR. GROSS: Dr. Fleming has a response.

DR. FLEMING: Yes, I would like, while we still have David at the mike, just follow-up on Ralph's question that I think is a critical one, which is that not only do we need to understand whether there is an increased risk but we need to understand how that occurs based on duration of exposure. If we go back, for example, to some recent explorations of, for example, COX-2s and their effect on cardiovascular death, stroke and MI, I think it was the VIGOR and APPROVE trials that were prospective, randomized studies that are suggesting that while this relative risk is about 1.5, it does seem to be dependent on duration of exposure. In fact, it becomes more substantial after accumulation of maybe 18 months. You really need a time zero cohort to be able to assess

basically when you are exposed to an intervention versus not. Followed ahead over time, is there, in fact, not only an increased risk but is this time dependent.

Dr. Andrews was saying we will make assessments on cases over person-time. Well, that analysis assumes a constancy of risk with duration of exposure. If that is true, that is a nice, simple analysis. If that assumption is not right then that analysis is misleading.

David, from your response, my understanding of your response is that you don't have any specific evidence in what you have done to allow us to understand whether there might be a duration of exposure issue.

DR. GRAHAM: Right. In addition to duration, there is also the question of dose. With rofacoxib, for example, there is no question that risk would increase with higher dose and the apparent evidence of the increased risk manifested itself with shorter durations of use and with the lower doses. So, there are basically actually two

parameters.

In terms of duration, I think that, you know, it would be wonderful--we have no problem I think establishing T-nought. So, for these inception cohorts we are able to identify the start of our observation of risk and I feel pretty comfortable that we are able to do that sort of within the limits of epidemiologic practice. The way we would do it I think would be widely accepted within the epidemiologic community.

The question is, as you can see from those persistency curves, that we don't have a lot of use, say, beyond 24 months. In that time period between 12 months and 24 months we may have sufficient use to say something but I think our power is going to be substantially reduced. So, in terms of the analytic plan, doing, say, a traditional survival time to event analysis, which would be my preference, I am not sure that we are going to have sufficient power. We may be able to sort of create strata. So, it is basically kind of a Kaplan-Meier version only we are going to have

wide intervals. You know, maybe we would look at the first 8 months or the first 6 months of treatment and then we would go in 6-month aliquots or something like that. Then we would lump everything from 12 months on because we have such low power.

But I think we are going to be stuck with that. So, I think something for the committee to remember is that the databases that we have in our program, the Ingenix database and the Kaiser database, are number one and number two in terms of size in the United States. In terms of quality of data, the Kaiser database is probably the highest quality healthcare database that we have for research purposes in the United States.

So, what I am talking about from a feasibility perspective is that there are some other large healthcare databases that FDA does not have direct relationship with through a contract mechanism that maybe could be recruited for a study like this. But for the base population that we are talking about we have 150 million person-years of

observation. So, I guess what I am saying is that we are probably running up against the limits of the prevalence of exposure and the background incidence of some of these disorders. I am sorry I can't be more helpful than that.

DR. GROSS: Dr. Furberg?

DR. FURBERG: I have a couple of comments. Is the mike on?

DR. GROSS: No.

DR. FURBERG: Thank you. I have a couple of comments. One relates to international comparisons and we haven't heard anything. I would like to know whether the prevalence of ADHD is the same in other countries. This can't be a unique U.S. problem but so far there is nothing on that. If so, what is the drug utilization in other countries? That could help us determine whether there is over-utilization or under-utilization of these drugs.

But what I am primarily interested in would be the experience in other countries in terms of serious adverse events. Adderall was taken off

the market in Canada--was it a year ago?--at least temporarily, and we haven't heard anything about that information. So, that would be helpful.

The other one was a question for David. He left me a little bit puzzled. The median use of treatment was 8 months and that raises some questions. Why is that? We are talking about a chronic condition. Is that because treatment is not very effective so people stop because the drug doesn't work? Or is it the opposite, they improve and they stop taking it after a while? Or do they stop because they have adverse effects? I think that would be useful.

The third comment relates to how we deal with co-existing cardiovascular conditions, whether it is abnormalities or presence of disease. I have problems when people say I am excluding those from analysis or doing some adjustments for it. In my book, people who have cardiac conditions are probably more susceptible to suffer adverse events and when you exclude them you miss that information. You miss it. The way to do it is to

include them in the study and stratify the analyses and then you can get the proper answer. But, David, do you have a comment on the 8 months?

DR. GRAHAM: I will just talk loudly because this mike is not working.

DR. GROSS: There is a different mike over here.

DR. GRAHAM: Is it working? Really? Curt, this is a mental status exam. You gave me three questions and some of them had a lot of detail to them. I will try to answer them the best I can.

The first one is dealing with how is this drug used overseas. In the United Kingdom they don't recognize ADHD as a disorder. So, if you look in the general practice research database for the use of these drugs you find that they are not used very much. That is the best source of information to look at. There really are no other--well, there are several databases in the U.K. that are based on general practices where one could look at this question, but there are no

databases in other countries than the U.K. where one could go to look at this. So, we are limited to what happens in the U.K.

Related to Canada, I will let people sitting at the table talk about the regulatory side of things but I would make this observation, which is that in every situation where we have had the opportunity to look at drug use in the United States and compare it to Canada we find that they are virtually identical. So, you almost sort of have--excluding Mexico--a North American effect on treatment patterns and practice of medicine, at least so far as the use of medications is concerned.

Your second question I think dealt with--

DR. FURBERG: The median use.

DR. GRAHAM: The median use, right. There are a couple of potential explanations. One is that we showed just everybody in our persistency curve, regardless of their duration of presence in the database. So, if you remember, I talked about turnover in the database so during the first year,

for example, in the different debases there can end up being, over the course of a year, an 8-30 percent turnover. That turnover doesn't happen sort of in a continuous fashion. It happens sort of at one-year intervals when people renew their health insurance. So, that undoubtedly accounts for sort of a shortening of the median duration. By how much, it is hard to say. Probably not by a terrible amount.

One thing which we could do, which we didn't have time to do but we will do is to take the people in our inception cohort, identify everyone within the inception cohort who is present in the database for a period of, say, two years and then redo the persistency curves. I think at that point we would get a more accurate reflection but there is no doubt though that there is a fairly steep drop-off.

That question sort of comes up then, and it puzzles me too and I don't have an answer for why did they stop. Well, it may be side effects. It may be that at the end of the day they decide,

or their parents decide, it is easier to live with whatever the behavioral disruptions are than to live with the drug. Children outgrow this. It may diminish with age but I don't think it abruptly ends within a year and it suddenly goes away. And, the drugs certainly don't cure the underlying disorder because in studies where people are on the drug and then it is withdrawn the behaviors return. So, I think that sort of addresses the second concern.

Then you third comment, I agree with you completely that we shouldn't be throwing anyone out of the study and if it turned out, for example, that the people at greatest risk for, let's say arrhythmia and sudden death, maybe through autopsy studies or through previous diagnoses showed that there were disorders that could be identified--congenital heart disease or who knows what--that would be very important because then it might actually then sort of become a condition of practice that certain studies need to be done in children before you start these drugs because if

they have, you know, this particular underlying condition their risk of sudden death is increased 100-fold. I mean, that is theoretically possible, that the risk could be concentrated in a small group, but we don't know that. But you are perfectly right that we have to pay careful attention to the subgroups and, you know, I would fight tooth and nail against throwing anyone out, as would you.

DR. NISSEN: Tom, you had raised the issue of the constancy function. I know you are sitting there, making some calculations on that famous yellow pad of yours. We know some things that may be helpful here. One of them is that for drugs that increase drug pressure, events like hemorrhagic stroke appear to happen at a relatively constant rate and probably very early. Stroke, similarly, probably has a very even constancy function. Myocardial infarction does not. It is very important if you look at, you know, blood pressure differences. There is an accumulating risk that takes place over time with blood pressure

shifts and myocardial infarction. And, we actually have some observations that may explain that. For example, we have looked at IVIS studies and we have seen that increasing blood pressure increases the progression rate of underlying atherosclerosis. So, in the adult population, the longer you have increased blood pressure the more you are accumulating atherosclerosis and the more likely you are, therefore, to be at risk of the MI. So, this issue is different for the different endpoints and that must be considered as we think about a potential trial.

DR. MANASSE: Much of our attention has focused on population-based epidemiological research and, I wonder, with the advent of a better understanding of pharmacogenomics whether we also might begin to consider some molecular research. What responsibility do the sponsors have in determining the underlying metabolic and genetic pathways here that might become predictive to the kind of events that Dr. Nissen relates to? I would be interested in hearing from the agency about the

discussions that are held with sponsors about getting a better understanding of that molecular basis for what we are talking about.

DR. GROSS: Anyone from the agency want to respond?

DR. LAUGHREN: Certainly, we expect sponsors to understand fully the metabolism of their drug and the genetic differences that might determine different metabolism. In terms of other pharmacogenomic explorations, since we don't understand for any of the psychiatric disorders the path of physiologic basis or molecular basis of these disorders, it is very difficult to lay that on them as a requirement. We are very interested in pharmacogenomic explorations and we are trying to get companies more interested in that, but it is hard to make that a requirement when we have virtually no understanding of these illnesses at that level.

DR. GROSS: Dr. Hennessy?

DR. HENNESSY: Thank you. David Graham and Elizabeth Andrews both gave very thoughtful

presentations and I just wanted to make a couple of incremental comments on those. One is that I think the most likely scenario, based on what we know about the pharmacology of the drug, is that there is a small increased risk in a subset that may or may not be detectable epidemiologically. In my view, the relative risk is certainly less than 5 and probably less than 2. A relative risk of 2 in a low risk population has a markedly different public health impact than the same relative risk in a high risk group. Therefore, I think presenting the power calculations in terms of risk differences and number needed to treat would be beneficial.

Third, I would consider a case crossover design as a supplemental approach. Fourth, for identifying deaths, the Social Security Administration death master file is less costly than the National Death Index, with the downside being that you don't have cause of death. Fifth, I would restrict studies of stroke to hemorrhagic rather than ischemic stroke.

The next point is that I think $900,000

for all the FDA cooperative agreements is a disgracefully low sum. Next, most of the pediatric spontaneous reports that were provided in the packet were associated with exercise. Because of that, I think that the highest risk may not be early on. It may be that a number of these events are exercise-induced and until that occurs in the patient it might not be observable.

Next to last, I think that because nobody thinks that these drugs might reduce the risk of these events, a one-tail statistical test would be a valid approach. Finally, I agree with earlier comments that, in parallel with the risk measurement exercise, a benefit measurement exercise needs to be put in place.

DR. GROSS: It is 11:30. We are supposed to have lunch so we are going to break for lunch now. If there is anyone in the audience who is going to speak at the open public hearing who has not signed in yet, please do so.

[Whereupon, the proceedings were recessed for lunch at 11:30 a.m., to reconvene at 1:00 p.m.]

A F T E R N O O N P R O C E E D I N G S

Open Public Hearing

DR. GROSS: The system has been fixed. It turns out the problem was that there were too many mikes so you will see a few less mikes around the table, therefore, we will have to share. So, that is the plan for the afternoon.

We are going to begin with the open public hearing. 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 advisory committee meeting, the FDA believes that it is 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 that you may have with any company or any group that is likely to be impacted by the topic of this meeting. For example, the financial information may include

a company's or a group's 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 relationships. 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, we will begin with speaker number 1, who is on the telephone, and that is Georgia Grossman. Georgia, are you there?

MS. GROSSMAN: Yes, I am.

DR. GROSS: Please carry on.

MS. GROSSMAN: Okay. I made some notes and I am going to try to read from them. I am the mother of Samuel David who died at 12.5 years old because of Ritalin. Ritalin was my son's death sentence. Sammy was the healthiest of my boys except for his low muscle tone which caused him to be slow in walking, running and speech. Physically, he never got any colds or any of the

childhood diseases, although his brothers got the measles, mumps and chicken pox, and he never was diagnosed with any heart problems prior to Ritalin.

No one in my family has ever had heart disease. We took him to a neurologist for his slow development for a complete evaluation to see if he could get physical, occupation and speech therapy. Instead, he was put on Ritalin for ADD, which we did find out later he never had. It took four years for Ritalin to kill my son. The last two years of his life he caught many colds and his school doctor said he had heart arrhythmia, but his doctor said the drug was causing this and it was nothing to worry about.

He was put on Ritalin in the fall of 1982 and died, riding his bicycle, September 5, 1986. The doctors had assured us that Ritalin was safe to take and we completely trusted them. No one had ever read the warning label on Ritalin until my son died. Then we found out he had most of the side effects of this drug. The autopsy on Sammy showed his heart was three times larger than it should

have been because of the arrhythmia.

From 1984 until 1986 Sam had most of the side effects of this drug. He had heart arrhythmia. He had a seizure at school one year before he died, which he had never--we have never had seizures in the family. He became very emotional, cried easily, something he had never done even as a baby. He became pathetically thin and we never knew the side effects of this drug.

This drug not only killed my son, but it has almost destroyed my entire family, consisting of eight adults and four children, and it devastated many of my son's teachers, friends and acquaintances. It has been almost 20 years since my son passed away and none of us are still over it.

DR. GROSS: Thank you very much. Speaker number 2? The names of the speakers, for the people at the table, will be up on the screen.

MR. LIBBEY: My name is Clinton Libbey, and I am here today as a volunteer member of Ablechild, a national non-profit organization

comprised of parents personally affected by, and greatly concerned with the issues of psychotropic drugs being prescribed to our children, and the erosion of full informed consent.

I have had first-hand experience with the labeling for ADHD and the drugs prescribed. As a concerned parent, I investigated the drugs that were being considered for my son, many of which are being reviewed by this panel currently. What I found was misinformation and distortions pertaining to both the subjective psychiatric labels being assigned to our children and the drugs being prescribed to them. As a result, it is almost impossible for parents to receive factual information on labels and drug effects, compromising their ability to make fully educated decisions.

When dealing with drugs that have known side effects, the oath of "first do no harm" must be transformed to "first do no harm without full informed consent." It is full informed consent that provides parents with the information that

they need in order to effectively make decisions regarding their children. This is especially the case when the treatment may cause the one side effect that is irreversible--death. When the diagnosis is less severe than the possible side effects full informed consent is critical and should not be adulterated in any manner.

I, for instance, was misinformed when several medical doctors told me that no one has died as a result of taking these drugs provided that they are taken in accordance with the dosage guidelines. I was also told that they are not addictive. I asked one doctor about a structural heart defect that my son had since it was contraindicated on the warning label. He told me that it is a common condition and that in a previous case they had a second opinion and prescribed the drug in the end. I was alarmed since it was specifically contraindicated and the doctor no longer considered it an issue.

Upon further investigation, I found parents who had, in fact, lost their children due

to these drugs, with autopsy reports directly linking ADHD drugs with their children's deaths. The fact is that children have died even though dosage recommendations on an approved label were strictly adhered to. I found many other parents who have had their children harmed by drug effects, which are often marked on the label but down-played by many in the medical profession. All too frequently, risks are not disclosed to parents seeking to make the best possible decision regarding their child.

As a society, we must disclose potential side effects prior to treatment in order to guarantee an individual's right to full informed consent. Strict adherence to this principle also transfers a significant amount of liability to the individual and is, therefore, good for all parties involved.

As a result, I am here to argue for action that will allow concerned parents, such as you and me, to make informed decisions regarding the drugs being prescribed to our children. The American

Medical Association couldn't have said it any better when, in 1999, they were quoted: Informed consent can be effectively exercised only if the patient possesses enough information to enable an intelligent choice. Ignorance is not bliss when you are a parent.

While many say that there needs to be more research on these drugs, I, with parents that make up Ablechild, many of whom are victims of the effects of these drugs, find that stronger warning labels and stiffer guidelines regulating full disclosure would be a more appropriate step. Furthermore, MedWatch filings should be mandatory for adverse reactions within the pediatric population.

The following victims of ADHD drug effects should stand for itself and the realization that if even one more child were to die due to these drugs it would be one too many: Shaina Dunkle, 1991-2001; 10 years old. I am also submitting testimony from her parent to the committee. Stephanie Hall, 1984-1996, 11 years old; Matthew

Smith, 1986-2000, 14 years old; Samuel Grossman, 1973-1986, 13 years old; Raymon Perrone, 1975-1995, 10 years old; Daniel Ehrlich, 1970-1984, 14 years old; Rylia Wilson, 1995-2001, 5 years old. Please don't allow another child to lose their life without at least warning their parents. Thank you for your time and consideration.

DR. GROSS: Thank you. Speaker number 3?

MS. LIVERSIDGE: My name is Ellen Liversidge. I have no financial relationship of any kind with this committee. I am a member of the Alliance for Human Research Protection, and the mother of a wonderful son who died of profound hyperglycemia following ingestion of an typical antipsychotic drug which he took for two years.

My son died in 2002, back before the FDA required a warning on the label of the drug but after other countries, of course, had required such a warning. The FDA finally required a warning a year after my son died, in 2003. I am speaking on behalf of myself and of all the other parents I have come to know who have lost their children to

psychotropic drugs, most of which drugs did not carry a warning. They live all over the country and would wish to be here testifying today but, of course, were unable to attend. I live nearby so I came on their behalf. Many of them did come to the SSRI antidepressant hearings. Fortunately, there is now a warning on those drugs--too late for their children but at least providing a caution for other parents.

I grieve particularly today for the 51 dead of ADHD drugs that were announced yesterday by the FDA. I guess my up-front message, front and center, is that you know that ADHD drugs can cause serious side effects and death, including sudden death, hypertension, myocardial infarction, stroke, and possibly bipolar disorder. This being the case, I urge you to recommend that these drugs have an appropriate black box warning placed on the label starting immediately. The FDA is notoriously last or among the last of the large westernized countries requiring warnings on labels, and thousands of people die or suffer as a result of

this inaction. I was appalled, for example, to hear Dr. David Graham say that the FDA knew for three or four years that the atypical antipsychotics were causing deaths in the elderly with dementia and Alzheimer's before the FDA required a black box warning against this off-label use.

I hope that this committee, in addition to recommending a warning, will recommend the following: The committee, in recognizing that there is a complete absence of any objective diagnostic test for ADHD and complete absence of any credible evidence regarding biological abnormalities in children diagnosed as ADHD prior to drug treatment, must take extra responsibility to ensure that the FDA is taking all necessary precautions to guarantee the safety of the drugs it recommends for approval for the treatment of this "condition."

DR. GROSS: Thank you. Speaker number 4?

MS. PARRY: Thank you. Good afternoon. My name is Sue Parry. I traveled here at my own

expense from New Mexico because I am concerned about the safety of the stimulant drugs given to children, some as young as two years old,

I have worked as a school-based occupational therapist with students, mostly boys, who supposedly had ADHD. I am also the mother of three sons who a decade ago, like many young boys in America, were at risk of being labeled ADHD.

Much of the information given to parents about ADHD then, and now, is confusing, inconsistent and contradictory. They are told that ADHD has biological underpinnings; that it runs in families; and that brain imaging studies reveal differences in the areas of the ADHD brain that govern concentration and impulse control.

They are often told to have their child screened at an early age because ADHD, if untreated and undetected, can have a negative impact on academic achievement; that they face a much greater risk of developing a comorbid disorder; and that they are at much greater risk for early substance experimentation and abuse. Meanwhile, the

psychostimulants, as well as other drugs, are routinely portrayed as benign, mild substances that are not associated with abuse or serious side effects.

What are these parents and teachers not told? They are not told that Ritalin is classified as a Schedule II drug, the strictest category of potentially abusable drugs that doctors can prescribe, or that Ritalin is chemically similar to speed, crank and crack cocaine, all drugs with devastating addictive potential. They are not told that the adverse side effects of stimulants are numerous, including insomnia, decreased appetite, stomachaches, headaches and nervousness.

Parents are not told that five subcommittee hearings have been held in the House of Representatives between 1996 and 2003; that at the subcommittee hearing in July, 1996 Dr. Debra Zarin stated: A myth surrounding the treatment of ADHD is the paradoxical calming effect of stimulants such as Ritalin. It is a commonly held misconception that if a stimulant calms a child,

then he must have ADHD. If he didn't have the disorder, the thinking goes, the medication would not have any effect. That is not true. Stimulants increase attention span in normal children as well as those with ADHD. Six years later, Dr. David Fassler, in 2002, made the same statement at another hearing.

Parents are not told of the possible future harm that may result from the diagnosis, as eloquently described by Dr. William Carey who states: The label may be stigmatizing and harmful in the long term in ways that are only dimply appreciated today. The diagnosis of brain malfunction, which seems so useful and comforting today, may at a later time come back to plague the person. We have not yet had sufficient time to observe fully the possible consequences it may have for education opportunities, employment, the military service or security clearances. Labels stick firmly, especially when they involve neurological disability.

Parents are not told that the 1998 ADHD

Consensus Development Conference statement reads: However, we do not have an independent, valid test for ADHD, and there are no data to indicate that ADHD is due to a brain malfunction.

The ADHD epidemic is a disgrace. Our nation's children do not need more federal studies. What they need is a federal grand jury to investigate what may be the biggest healthcare fraud our nation has ever seen. Only one government agency, the DEA's Office of Diversion Control, has stood up to this psychopharmaceutical cartel.

Is the ADHD epidemic about neurotransmitters and chemical imbalances or is it about increased market share for drug companies, increased funding for research and increased business for medical entrepreneurs? Have our kids simply become funding mechanisms to be screened, labeled and medicated? Thank you.

DR. GROSS: Thank you very much. The next speaker, speaker number 5?

DR. GRIFFITH: I am Dr. Chris Griffith.

It is truly a privilege and honor to be here with you today. I am here as a representative of CHADD, Children and Adults with ADHD. I also represent the membership of the National Medical Association.

To tell you about my experiences in treating and evaluating ADHD and other childhood mental health conditions, my experience could perhaps be best described as broad and diverse. I currently maintain two clinical appointments, both to Emory and Morehouse schools of medicine. I am in private practice in suburban Atlanta, and also provide services to a community mental health center in DeKalb County, Georgia. I see the full spectrum, all the faces of ADHD. Prior to coming here as well, I spoke with numerous colleagues throughout the country, and would like to believe that I am a representative of the everyday practitioner that treats ADHD, a medical disorder.

Cardiovascular safety and general cardiovascular safety continue to be of the highest concern for CHADD and membership of National Medical Association when we are prescribing

medications for the treatment of ADHD in children and adolescents. My comments are in no way to disrespect or offend any parent, child, of loved one who has lost someone due to an untoward, rare cardiovascular complication whether it be from ADHD medication, penicillin, or going in for a routine dental procedure. Generally, these medications are safe and effective, both stimulant and non-stimulant medications. A number of these medications have been used for greater than 60 years. We, as physicians, know what they do; we know what they don't do. The cardiovascular side effects that occur typically are mild and rarely severe or life-threatening. Again, this is so important to remember--that medications are not innocuous and we need to consider care in prescribing and treating.

The most common challenge that we face as everyday practitioners is really this, it is not so much the complications of cardiovascular side effects but it is more related to the dangerous, potentially life-threatening complications of

failing to recognize and treat this devastating condition.

The next series of challenging questions, hopefully, paint a picture for you on what this condition may masquerade itself as. Look at the risk and benefits of treating versus not and, as well, the importance of early diagnosis and recognition of symptoms. I hope as well that the passion of the National Medical Association and CHADD are expressed through these comments.

Here is the question I want you all to consider. It is this, it is about what happens. What happens when a child loses all hope and ambition; what happens when it is easier to find a vial of crack cocaine or 40 ounces of beer as opposed to a park or community recreation center? What happens to a future generation of minority youth, African-American, Latino males who disproportionately populate our juvenile justice system? What happens to a teenager's sense of fun when we are dealing with high rates of teen pregnancy, sexually transmitted diseases and even

abortions? Finally, what does it say about all of us? We turn on the news each night and we tragically see young drivers, teenagers, killed in automobile accidents--so many that we forget their names, their faces and their stories. We develop a sense of apathy.

This may all seem like drama. Unfortunately, it is the untold story of what happens when we fail to recognize and treat ADHD. With untreated ADHD we see higher rates of school and occupational failure; greater rates of incarceration; juvenile delinquency; substance abuse; teen pregnancy; sexually transmitted diseases; more problems with depression and self esteem and, finally, greater numbers of automobile accidents and fatalities.

In my opinion, the greatest concern involving safety of these medications has more to do with who is prescribing them and how it is being done. Over the past several years there has been a progressive deterioration in the ability to find comprehensive child and adolescent mental health

services. This even includes lack of access to certain medications. Misinformation, disinformation, lack of education poses a big danger as well. These findings are supported by the Surgeon General's report of 1999, who further added that some of the greatest disparities in healthcare occur in minority populations, inner city and rural areas. Commonly the restriction to care may be governed by economic or geographic constraints.

In summary, the medications used for treatment of ADHD are safe and very effective. Clinical judgment and wisdom as a physician comes through long hours, thousands of hours of learning and clinical experience. For each doctor, the special skill and tool, hopefully, remains our most valuable weapon in the arsenal as we treat ADHD and other children healthcare conditions. Please keep in mind those dire consequences of what happens when we don't adequately address and treat this condition.

CHADD and the membership of the National

Medical Association respectfully request that no additional restrictions be placed upon the usage of these medications. We feel that the health and welfare of patients in the highest need would be adversely affected by additional warning labels or restrictions. Thank you very much, Dr. Christopher Griffith.

DR. GROSS: Thank you. Speaker number 7?

MS. LUCAS: Good afternoon. My name is Sandra Lucas, and I am here to speak on behalf of the Citizens Commission on Human Rights, the psychiatric watchdog established in 1969 by the Church of Scientology.

I think that the prevalent thought for the day, as expressed by the members of this committee is that studying this particular issue is problematic, and there does not appear to be an actual defined solution to this problem. Yet, we do know that the side effects of the stimulants are not only present, they are extremely serious and sometimes lethal. So, while the FDA ponders the problem of studying the issue and conducting the

studies that may have inherent flaws, what real, immediate protections are to be put in place for parents and children?

If anyone proposed to study the issue of giving cocaine to children to suppress symptoms of inattention, that individual would be regarded as off his rocker, for lack of a better expression. Yet, there is already ample evidence that stimulant drugs given to children are similar in their effects to cocaine, the major difference being, of course, that cocaine is illegal, that drug companies do not profit from it, while stimulants are legal and highly profitable.

So, while the FDA would not engage in a study of the effects of cocaine on the health of children, it is about to engage in a study of cocaine-like drugs. No less than a preemptive warning is called for today. It is a necessity and the only ethical decision that can be made. Medical professionals and decision-makers, such as parents, cannot afford to wait to be told the truth already known. The lives of many children are at

stake. A preemptive warning is also needed at a time when public confidence in the FDA is at an all-time low.

Conflict of interest between several members of numerous committees have been exposed. In fact, I can think of one member from previous committees who was so beholden to the drug companies that one might liken his presence to any hearings to inviting Osam bin-Laden to a national security meeting.

We must ensure that the tail no longer wags the dog. Parents' and children's interests must come first and, since we were talking about disclosure earlier, it appears that the gentleman from CHADD may have forgotten to disclose his tie to Novartis. Thank you.

DR. GROSS: Thank you for your comments. Speaker number 8?

DR. GREENHILL: Good afternoon. My name is Lawrence Greenhill. I am a child psychiatrist, a member of the American Academy of Child and Adolescent Psychiatry and the American Psychiatric

Association. My travel here was paid by the American Academy of Child and Adolescent Psychiatry and I have consultant relationships with Jansen and Novartis, and a number of other drug companies. You should know that. I think that that disclosure also should be accompanied by the fact that I have a large practice with children with attention deficit hyperactivity disorder and have spent my career studying the safety of drugs used to treat children. In that regard, I want to extend my sympathy to all the parents whose children have experienced adverse events, serious adverse events and, of course, as we have heard today death.

In my talk, I would like to make three points, and those points have to do with what has been discussed this morning, the benefit to risk ratio which must be considered by families before they take any treatment.

First is the benefit. We have heard debates about these medications but let me say that the evidence base for the use of these medications

is the largest for any behavioral treatment for children, with over 7,000 children and over 225 controlled studies over the last 50 years. When carefully diagnosed and treated, with full disclosure to the family, medications for attention deficit disorder produce robust responses in over two-thirds of affected youth by lowering the intensity of their attention deficit hyperactivity disorder symptoms. Children with ADHD can sit, concentrate in class and are less often rejected by their peers.

The medications we are discussing today are the largest group of medications approved by the Food and Drug Administration for the treatment of children with behavioral problems. Although I think we are having a good debate about their safety and their utility, the fact that they are approved gives the agency a chance to further define the risk and, hopefully, further define the benefit.

My second point, as with all effective treatments, attention deficit hyperactivity

disorder medications are associated with adverse events. These adverse events come in different flavors, frequent, infrequent and rare. The frequent adverse events, those that occur in, let's say, 10-15 percent of the children who take the medications are the ones we have heard about--nervousness, decreased appetite, delay of sleep onset, headaches and stomachaches. Practitioners who talk with the families of the kids they treat find out and adjust the doses, change the medication and, in most cases, can deal with these adverse events.

The middle category of children involve more worrisome kinds of problems such as tics, and the rare events, 1/100,000, involve serious, unexpected and tragic adverse events which we are learning about today, the cardiovascular events and sudden death.

Now, in an effort to try to work on this problem, one should consider the third point that I am making, which is to try to use currently existing cohort studies, registries and practice

networks to gather information of a kind that would give families and physicians a better ability to balance...[the speaker's time runs out]. Thank you.

DR. GROSS: Thank you very much. The next speaker is number 9.

MR. JONES: Hello. My name is Allen Jones. I am here today as a board member for the Alliance for Human Research Protection. In the interest of full disclosure, I will add that my career as an investigator was destroyed when I went public with information concerning corruption in the marketing of psychotropic drugs to public health systems and institutions.

My criticism of the Texas Medication Algorithm project, the Teen Screen and the new Freedom Commission has been widely reported. I sincerely hope this panel will place the health and safety of the American people above all the loyalties you may have. Some of these loyalties may be to the drug industry which has been generous to you in the past.

I look at this panel and I am troubled. Most of you have had past or current relationships with the drug industry. I spent time researching these relationships and will make those results available to any interested press entity. Some of the relationships are slight. Some of them are old; some of them are not. How many in the back of the room know that Dr. Elizabeth Andrews, who spoke earlier, is a past world vice president of GlaxoSmithKline? How many in the back of the room know that Dr. Manasse heads an organization that takes in millions of dollars from the pharmaceutical industry? These things were not, to my knowledge, disclosed.

I look at this panel and I am troubled. Is the safety of America's children in the right hands? This panel will decide that. The FDA has been criticized for seeming to maintain a deliberate ignorance of drug side effects and adverse events that are readily apparent in hospital emergency rooms, case reports in the medical literature and doctors' offices around the

country, and the reporting by regulatory agencies in other countries. Pharmaceutical marketing in the United States seems to have far outstripped the willingness of the FDA to track adverse events.

There is urgency in this present situation. Millions of Americans are taking drugs that threaten their lives. They are unaware of the dangers. In large measure their doctors are unaware of the dangers. We are not unaware of those dangers. The FDA must take immediate and decisive action to make the medical community and American citizens aware of the risks of these drugs. We cannot rely on future clinical trials to save the persons who are at risk today. We must thoroughly and vigorously use the resources we have available to address the current danger.

The MedWatch system is criticized for picking up only 1-10 percent of adverse events and, yet, the flag for those events has led to this meeting today. I urge the FDA to immediately and decisively employ this resource to gather data relative to the real-world consequences of these

drugs.

The Alliance for Human Research Protection requests the FDA to issue a public advisory, a "dear doctor" letter to every doctor in America to apprise them of the essentially lethal side effects that are being tracked, and to solicit the reporting of any and all adverse events of which they are aware. If the FDA does not have the mailing list, I am sure industry can provide it.

The FDA should demand that industry immediately advise the FDA of all adverse events that have been reported concerning these drugs, and should demand that all clinical trial in possession of these companies be presented to the FDA so that independent researchers can search them for markers and adverse events.

We don't have the luxury of time to wait for the future trials. Children have died. Children are dying. We must act today to begin mining the adverse effects data to fully assess the adverse events that have occurred and been reported.

These steps will require more political will than the FDA has required in the past. Your panel recommendations today will determine if past mistakes are repeated or remedied. Industry's interests in influencing policies, reviewing process and selection of efforts has no purpose here today. I ask you to put your own interest aside and protect the children of the United States of American.

DR. GROSS: Thank you. Speaker number 10?

DR. GRUBER: Good afternoon. My name is Dr. Todd Gruber, medical safety director for Novartis, and I am here today to read you a short statement about the Novartis ADHD medications:

Ritalin, known generically as methylphenidate, has a long record as a safe and effective medication for the symptoms of ADHD. It was approved by the FDA in December of 1955 and for more than 50 years it has helped patients and their families lead more productive, healthy lives. Ritalin is the most studied drug for ADHD and patient exposure amounts to more than 8.4 million

patient-years of treatment.

In addition to Ritalin, other methylphenidate products have been available generically for many years. In recent years methylphenidate has also been available in several long-acting products from Novartis and from other manufacturers. We would also like to note that although methylphenidate products and amphetamine-based products are in the same class, there are some differences between these medications, as well as some of the other ADHD medications.

Novartis is committed to patient safety and adheres to rigorous monitoring standards to evaluate the safety of all drugs in its portfolio. For all of its products, Novartis reviews the global safety database as well as the literature on an ongoing basis.

With respect to cardiovascular events, Novartis has reviewed its spontaneous report safety database for methylphenidate and submitted its findings to the FDA. Our review included data from

over 50 years and found that there does not appear to be any increase in cardiovascular events associated with methylphenidate use when viewed in the context of rates in the general population. In patients with certain preexisting cardiac conditions, the labeling for methylphenidate and other stimulants currently includes a recommendation advising caution. We will work closely with the FDA in developing any additional labeling changes as necessary.

We commend the FDA and this committee for discussing how to address further studies in this area. We welcome the opportunity to participate in subsequent discussions with the FDA and with other manufacturers about any recommendations resulting from today's discussion. Thank you.

DR. GROSS: Thank you. The last speaker, speaker number 12?

DR. ALLEN: Good afternoon. My name is A.J. Allen. I am the medical director for Strattera at Lilly globally.

Like the FDA, Lilly has concluded that

both clinical trial data and post-marketing reports have limitations when evaluating cardiovascular safety. So, we have grappled with similar questions to those that you are addressing today.

I am going to briefly present the methodology that we have selected for a study that our safety group is currently conducting. We expect to have final results in the next few months and will share those with the FDA. I have outlined on this slide some of the characteristics that we believe are important considerations when designing a study to evaluate cardiovascular safety. I am just going to highlight a few points on this slide and others.

Any study needs to be well controlled, both for possible biases and treatment assignment and for other factors. It needs a large number of real-world patients so it is clinically meaningful and so that it is possible to detect rare events. Finally, results need to be available quickly, within months, not years. As in any area of science, there is no one ideal study and the data

need to be considered, once they are available, in light of other data, including treatment benefit as well as risk.

Lilly believes that a retrospective cohort study of adults using health claims database from a large U.S. managed care population is the best option for a number of reasons. While not as well controlled as a double-blind clinical trial, propensity score matching provides a means for minimizing biases introduced by non random treatment assignment. Matched cohorts of patients treated with atomoxetine and stimulants can be compared to each other and to a general population cohort. The sample is large and generalizable to the U.S. adult insured population. Adults are at greater risk for cardiovascular events so the chances of detecting a possible signal are greater. Finally, the data are available so results can be obtained quickly.

The objective of this study is to estimate and compare cardiovascular and cerebrovascular outcomes in three cohorts of patients, those

initiating therapy with atomoxetine; similar patients initiating stimulants; and age- and gender-matched general population cohort. The outcomes include cardiovascular adverse events and myocardial infarction as well as all-cause mortality. We are using diagnostic and procedure codes in medical claims to identify the outcomes, and there is a clinician review of claims, although not of medical records.

We are using propensity score matching to attempt to control for the fact that in an observation study treatment selection is non-random. Doctors choose to treat patients with different medications based on the baseline diagnoses, other medications that they are receiving, etc. Propensity score matching in this case uses information from the prior six months to match patients in part of the cohort entry. The goal is to have two cohorts that are very similar in their characteristics with respect to initiating atomoxetine or stimulants.

We don't have final results but we have

some feasibility data that was recently completed. I would like to use this to make a couple of points. This column is percent in the age- and gender-matched general population. This is stimulants and percent on atomoxetine before propensity score matching. These are the percentages after propensity score matching, and these are diagnoses at six months prior to baseline.

There are a couple of important points here. Note that patients treated for ADHD have a higher percentage, in some cases dramatically higher percentage of baseline diagnoses as compared to those on the stimulants--I am sorry, on medications. In addition, the differences are minimized when we match with propensity score matching.

There are limitations to this study. I won't go into those in detail. This is a study in adults. This is a study that uses propensity score matching which is not a perfect means for correcting for this, but it does help, and this is

also not a study that uses clinical data. Thank you.

DR. GROSS: Thank you. At this particular point I would like to ask if there is anybody else in the audience who would like to make a comment. Yes? Please identify yourself when you come to the podium.

DR. ROBB: My name is Dr. Adelaide Robb. I am a child psychiatrist here, in Washington, D.C., at Children's National Medical Center. I am here as the second speaker for the American Academy of Child and Adolescent Psychiatry, and I have done clinical trials for the ADHD indication for Shire, McNeil and Eli Lilly.

I wanted to make two points. Number one, earlier in today's presentation Dr. Graham had talked about the fact that in Europe they did not believe in ADHD and they did not treat it at the rates that we do in the United States. In fact, right now in ten European countries, at over 200 individual sites they are doing a naturalistic observational study of ADHD in children ages 6-17.

It is known by the acronym ADORE, which is ADHD Observation Research Europe. They are following children as they come to clinician's offices to see what happens to them as they are treated either with therapy, educational interventions or medication across time, both in terms of their ADHD symptoms, as well as their quality of life. That study was starting to have some reports out at the child psychiatry meetings held in Toronto last October, and it will continue to be another source of information about ADHD in other parts of the world, and perhaps the committee might want to take a look at the things that were presented.

The second thing I wanted to talk about is taking care of children with ADHD who also have underlying cardiac or blood pressure issues. As a tertiary care center in Washington, D.C., we see kids who have congenital heart disease, who have hypertension because high blood pressure runs in their family. When they come in with comorbid ADHD and they need treatment--and tutors have not helped, and smaller classroom sizes, and extra time

with the teacher, and one-on-one instruction--all the things that in a cardiac patient you would try first rather than initially starting medication, when that doesn't work and this child is still flunking out of school and the child is intelligent enough to do better in school and is struggling with paying attention and working in the classroom, we work in conjunction with our cardiology colleagues to start the child out on a low dose of medication, get repeat electrocardiograms, get repeat blood pressure readings, and continue to monitor the child's progress in terms of their ADHD symptoms, as well as safety in terms of their cardiac condition.

I have one young lady who did have congenital heart disease. She still has that. And, she came to see me because she was flunking out of high school. This was a kid that wanted to go to college, was a smart kid and just couldn't get her homework done, couldn't stay on topic. I called the cardiologist and said I know she is your patient. We need to treat her ADHD. What do you

recommend? The cardiologist said of the three options that we had, methylphenidate, atomoxetine and amphetamine, methylphenidate had the best safety record in terms of safety in conjunction with cardiac disease. We started her out at a low dose of a long-acting methylphenidate preparation. We got serial EKGs. It is now three years since she started treatment. She is on the honor roll and she is about to graduate from high school and go to college. I think we forget about those kids when we are talking about the horrible tragedies that the other moms and dads have had, but I don't want children who have cardiac disease to not be treated because we are afraid we are going to harm them because then their school work suffers, and I think that is an important part of a child's life too. If they can't get through high school their opportunities in life are really diminished and we need to think about the benefits as well as the risks. Thank you.

DR. GROSS: Are there any other questions or comments from the audience? There being none,

we are scheduled for a break at two o'clock. We might as well take it now and we will reconvene at 2:15.

[Brief recess]

DR. GROSS: Dr. Gerald Dal Pan will discuss the questions that the group will consider, but before he goes on Jackie had a question that she wanted to have answered. So, Dr. Gardner, please proceed.

DR. GARDNER: Thank you. I actually have two and will ask for help on this. First, we have been talking today about ADHD medications as if they were go/no go situations, you look into a database and you either see them or you don't. My experience in the pharmacy and also anecdotaly with family is that there is a tremendous amount of concomitant prescribing, of sequential use and of multiple different drugs being used at different times during the week according to what school schedules are, and so on; also, trying to get a dose--sometimes they are using two strengths to get to the dose.

So, I think that we should understand the complexity a bit of what the prescribing and utilization of these drugs is if we are going to think about studying them in claims databases. To that, either now or as we go on in the discussions, I would like to ask Dr. Rappley for her help because she does prescribe these drugs and knows them very well. So, that is my first thing.

DR. GROSS: Why don't we answer that first and then go to the next?

DR. GARDNER: Deal with that?

DR. GROSS: Dr. Rappley?

DR. RAPPLEY: I think you raise an important point. When we look at data in terms of counts of prescriptions, people who either prescribe or receive these prescriptions understand that we often have to use multiple prescriptions to get at a single dose. For example, if I wish to prescribe 15 mg of methylphenidate I most often must write a prescription for 10 and a prescription for 5, unless the family wishes to break a 10 in half and often the school will not accept half a

tablet and will not engage in breaking tablets. Then the family has two co-pays for those two prescriptions, which can range in our area very easily from $40-50 per co-pay.

In addition to that, there are people who go in and out of eligibility in their insurance coverage and may be facing months where they do not have insurance coverage. For some of these medications the cost can be a few hundred dollars per child for the more expensive preparations, and probably the minimal cost even with generics is somewhere between $50-80 per month for prescriptions in our area.

So, I think that it is a complicated issue in terms of counting prescriptions. Prescriptions do not necessarily equate to per child. In addition, I think it is advisable to remain with the same product but we may use long-acting and short-acting methylphenidate or long- and short-acting dextroamphetamine preparations in order to target certain areas of the day or certain activities.

DR. GROSS: Thank you. Dr. Gardner, question number two?

DR. GARDNER: Question number two, we have talked a lot about information that we don't have today. In particular, Robyn asked about effectiveness and we haven't heard much about effectiveness. I know that there has been at least one NIMH-funded study of ADHD drug use in children, and I also noted that Dr. Greenhill, who spoke in the public comment period, was one of the investigators of that study. Results have been published so it isn't something that is being planned and I wonder, with permission, if Dr. Greenhill is still in the room if he would be willing to give us a summary of at least some of what is known about the effectiveness of these drugs to address Robyn's question and give us a little more information than we have had to date.

DR. GROSS: Dr. Greenhill, will you please assume the podium?

DR. GREENHILL: In answer to Dr. Gardner's question, I can tell you a little bit about the

work that was done in the multi-model treatment study of ADHD. It was an NIMH-funded study six sites across the country, involving 570 7-10 year-old children, boys and girls, with the combined subtype of attention deficiency hyperactivity disorder.

Unlike many of the trials that are run by this agency, this was not a study comparing treatment to placebo but comparing the relative effectiveness of different treatments. So, we had a psychotherapy arm, a medication arm, a combination of the two, and a community treatment arm or treatment as usual. What we found after 14 months of the study was that children in protocol did better than children in the community. Children who were on a medication protocol did significantly better in multiple domains than children on non-medication protocols. And, the addition of psychotherapy to medication provided slightly more benefit but nothing like the difference between medication alone and behavior alone.

The reduction of the ADHD symptoms was the first thing that was seen, and it was very clear with a large effect size, not a standardized unit of change. In psychiatry it is usual to have effect sizes between 0.5 and 0.7 standard deviations. Teachers saw changes in behavior in a double-blind, controlled component of the study which reached 1.2 standard deviations, which is a very large change. Not only were the ADHD symptoms involved but other domains were affected as well, such as parent-child relations.

We did a controlled study examining video-tapes and doing counts of a sub sample of families from each one of the sites and we found significant decreases in negative parenting. Those decreases in negative parenting proved to be mediators of improved socialization and learning in the classroom. So, we actually found a cross of domains, so, improvement at home in the family affected behavior in the classroom, but only for the children on medication.

From that study we concluded that in terms

of effectiveness the medications, which were very well tolerated, with less than one percent of the 288 who were carefully adjusted to their optimal dose had to discontinue the study--very well tolerated--provided the biggest improvement for these children in the area of academics, behavior, performance on achievement tests, performance on IQ tests and the impact on improving parent-child relationships.

So, we felt that we were able to support some of the findings from other studies that showed that the decrease in ADHD symptoms brought children who had severe ADHD symptoms into the range of control children who did not have ADHD. So, a blind observer looking at a classroom could not identify the child who had ADHD, at least based on the symptoms.

The final point I want to make is that it had an impact on peer relations in that the peer nominations that we obtained from the classroom showed that all the children who were in treatment, and the treatment was effective regardless of what

type it was, their peer nominations increased so that they were not as excluded from the peer group.

So, we concluded at the 14-month point that the children who were on the medication treatments had improved across a number of domains. Also, a majority of them failed to meet criteria for the diagnosis. After the study we followed them for 24 months and then 36 months, which we have reported also in studies. What has happened is that there has been no more treatment offered by the study group. We were just following them in a naturalistic way. What has happened is that all the groups have kind of drifted together. The good news is that the children who went through the MTA study are all better off in terms of their symptoms than they were before they came into the study. But the separation between the groups where we found more effectiveness with the medication and an advantage for being on the medication has decreased, as has their use of the medication. So, we are in the process now of interpreting and following them for a 10-year period and hope to

report on that.

The medication involved was methylphenidate and it was actually the immediate release, not the long duration that occurred before.

DR. GROSS: Thank you. Thank you very much. Dr. Dal Pan? Dr. Dal Pan will introduce the questions.

Introduction of Questions

DR. DAL PAN: Thank you very much. I would like to introduce the questions for this afternoon that will be based on the discussion that started this morning. I actually think the committee really started discussing some of these questions in the period that was allocated for questions in the later part of the morning. I hope to see that discussion continue.

I want to thank Dr. Gardner and Ms. Shapiro for bringing up the questions about benefit. We did not have a presentation on the benefit of this set of drugs. That would have involved quite an extensive presentation. I agree

that to discuss the risks of the drug you need to do that in the context of the benefit. If we were to come back and discuss the results of whatever studies come out of today's meeting, we would certainly have to discuss them in light of the benefits of the drugs. So, our not discussing benefit by no means places lack of importance on the benefit/risk relationship. Rather, we are here to discuss the best methods to study these problems.

With that, I am just going to go through the questions and read them. What I will do is I will read all the questions and then you can deliberate them under the direction of the Chair.

[Slide]

Question one is please identify and discuss the most important outcomes to study in both children and adults. In doing so, please consider whether the choice of outcomes differs by age; the validation of the outcomes in whatever type of study you discuss; and the selection of the appropriate comparator groups.

[Slide]

Question two is please comment on whether ADHD drugs should be studied individually or collectively.

[Slide]

Question three is on two slides. The background is on this slide. Which of the following approaches seems best to study cardiovascular outcomes with ADHD drugs? We are going to list them on the next slide but, in thinking of them, consider the methodological issues; the nature of the outcomes; the time needed to conduct the study; and cost issues in the following types of studies:

[Slide]

We have here a prospective case-control study, a case-control study in which we actually design and go out and do first-hand data collection; a large simple trial; a case-control or cohort study within a claims database; or other approaches that the committee considers.

[Slide]

Question four, what are the important confounders relating to use of ADHD drugs in both children and adults that should be considered in a study of ADHD drugs and cardiovascular outcomes?

[Slide]

Question five, discuss study approaches that may explore duration of use of ADHD drugs. Specifically, consider whether there are feasible study methods that could be undertaken to characterize longer-term cardiovascular risk, in any age group, with chronic ADHD drug therapy. Thank you.

Committee Discussion of Questions

DR. GROSS: Well, you always give us interesting challenges. Thank you. Dr. Nissen?

DR. NISSEN: Yes, at the risk of derailing us, I guess I want to raise an issue that is not in the questions. Let me see if I can pose this well. I am glad Bob Temple is here because I want to quote Bob in a minute.

What has happened here is that over the last decade or so we have seen an enormous rise in

the use of these drugs, now to the point where 10 percent of 10 year-olds are getting treated for this disorder. I figure about 1.5 million adults are getting treated and 10 percent are over the age of 50. To quote Bob Temple, we have a lot of priors on this class of drugs. We know that phenylpropanolamine and Ephedra and other drugs, very closely related, have yielded increases in stroke and other cardiovascular side effects.

So, I think we have to discuss right now risk mitigation strategies, not what we are going to learn in five or ten years but what we are going to do now, today about the problem. And, I think what we have seen is almost certainly over-diagnosis and overuse and we need to put some road blocks in the incredible logarithmic growth in the use of these drugs by making patients and their parents and physicians aware that giving sympathomimetic drugs, giving catecholamine-like agents has significant cardiovascular implications.

So, I want us to discuss the possibility of a new black box warning that says that drugs in

this class--other drugs in this class have been associated with death, myocardial infarction and stroke, sudden death, MI and stroke. I think we need a patient guide for parents. I think parents need to be informed about the risks of these drugs in a very clear way. No one is saying there aren't children, like some of the ones we have heard about, that are desperately dysfunctional and need these drugs but it is probably not 10 percent of 10 year-olds and it is probably not a million and a half adults.

So, I must say, I have grave concerns about the direction we are going in with the mass use of these drugs and the potential for harm and I think we can't just discuss future strategies. We have to discuss what should be done now to inform the public and inform physicians about what the risks are and what we can do about them. So, I want to put that on the table, if I may.

DR. GROSS: I think Deborah Dokken had a comment.

MS. DOKKEN: I think my comment wasn't

quite as explicit as Dr. Nissen's but I wanted to do this before we listed the five questions, to say that basically I felt there was a broader issue in the room which we perhaps cannot deal with today or perhaps it is not within the purview of this committee, but at least I would like to discuss the strategy for the broader issue and I felt that it did come back to Dr. Shapiro's earlier comments about benefits.

Something that I feel, is just as physicians and families have to balance benefit and risk, I think the FDA also has to balance when you put out information that isn't, you know, totally fleshed out and when you acknowledge that unless the FDA puts out some information it is going to come from another source. Once in another meeting I said that I thought the train was already out of the station and I suspect that a lot of information is already out now. You know, I think we do want to be in the position of being providers of information. In Dr. Greenhill's written statement he said something about information and only then

can the partnership of parent and practitioner make any informed decision about benefit and risk.

I guess that is my position. I think we need to trust that parents with good information are perhaps the best decision-makers for their children in collaboration with clinicians that they have a relationship with. So, I don't know, as I say, I am not clear since I am just a transplant to this group for the moment whether we address the issue or we come up with a strategy to have it go some place else and be addressed.

DR. GROSS: Thank you. Dr. Dal Pan, could someone from the FDA comment, for those of us on the panel who either didn't read all the words in the package insert--tell us what kind of warnings currently exist for the various drugs that we are discussing?

DR. DAL PAN: Yes, I will ask Dr. Laughren to do that.

DR. LAUGHREN: At the current time, all of the drugs approved for ADHD have either a warnings or a precautions statement basically cautioning

prescribers about treating patients with underlying medical conditions that might be compromised by increases in blood pressure or heart rate, for example, preexisting hypertension, heart failure, recent myocardial infarction or hyperthyroidism. It suggests further that blood pressure be monitored periodically in patients who are treated with these drugs.

Most of the labels go on to summarize the blood pressure and heart rate findings from the clinical trials in whatever particular program was done for that drug. In addition to that, as of I think August of 2004, the drug Adderall and Adderall XR have had warning language--let me just read it--basically stating that sudden death has been reported in association with amphetamine treatment at usual doses in children with structural cardiovascular abnormalities. Adderall generally should not be used in children or adults with structural cardiac abnormalities.

We have more recently asked all the other stimulant manufacturers to add similar language to

the warning section of their label so that all of the stimulant drugs at least will have consistent language. But I would point out that this is not a contraindication and I think this addresses a need that was brought up by one of the speakers. Dr. Robb described a patient with underlying structural abnormalities who was successfully and safely treated with methylphenidate. So, that is why it is not a contraindication but it is an alert to clinicians to pay attention to the effects of the slight increases in blood pressure or heart rate that patients might have with underlying disorders and to be cautious.

You know, we feel that this language is appropriate given our current level of knowledge about these drugs. I think it is a mistake to assume that we know what the risks are, and that is precisely why we are asking this committee to help us in trying to design a trial to better define the risks.

In terms of making labeling changes and other actions, I would point out to the committee

that we have another meeting scheduled of the pediatric advisory committee and the phsychopharm. committee next month to deal with some of these issues, both cardiovascular issues and psychiatric adverse events. So, this is not the only opportunity for an outside group to give the FDA advice about what to do with labeling. You know, we specifically sought this committee's advice on how to design a study that is going to help us better define the cardiovascular risks.

DR. GROSS: How would you make the determination to convert a warning into a black box warning? How is that decision made?

DR. LAUGHREN: In my view, we ordinarily reserve a black box for a risk which is very clearly established as causal and I don't think we are there yet with this cardiovascular risk. I really don't think we are there yet. We have a lot of cases. These are spontaneous reports, as you have heard. Many are very difficult to interpret and we desperately need to try and figure out a way to systematically confirm whether or not there is a

risk. I don't think we are there yet for a black box. That is my own personal view.

DR. GROSS: Curt?

DR. FURBERG: Well, I would like to speak up in support of what Steve Nissen said. We are here to discuss a problem and the solutions are both short term and long term. I think what Steve brought up was the short-term solutions and the long term are the ones that are in the five questions.

I think I understand the labeling. You have wording, descriptive wording. You have language under the heading of "warnings" and "precautions." My understanding is that the impact of those words is very minimal. In order to get a message across to physicians and patients you need to step it up a bit. I agree that we don't have final information on harm but sometimes what is missing in the labeling is a statement that these drugs may have a harmful effect; there is incomplete information; and advise caution. So, a little bit of that wording I think could be part of

it.

However, I take the view and support what Steve is saying, that I think that it would be reasonable to elevate the warning to the public and add a black box to it. The other one is a patient guide so that when parents are filling prescriptions for their kids they get a written document laying out the state of knowledge, or lack of the state of knowledge and the potential risks so they are reminded each time that there is a potential risk and we are trying to find solutions to it. I think that is fair enough.

I would just like to add to what Steve said. I am concerned about patients who have established heart disease, any cardiac condition. They are the ones that are very susceptible to all these types of drugs, sympathomimetic drugs, and I would like to see that almost as a contraindication for use.

DR. GROSS: My next question is--you answered the one on how you decide to use a black box. How do you decide when to issue a patient or

family guide?

DR. LAUGHREN: Well, there are several types of patient labeling that are out there. There is something called patient package insert which is voluntary on the part of manufacturers, and some of these drugs have these PPIs. A medication guide is something which generally is reserved for situations when there is a very specific risk that FDA requires a company to convey with a specific medication guide. The most recent example of that is the medication guide that was mandated for pediatric suicidality for the antidepressants. That was mandated about a year ago and implemented. Again, it was for a very specific risk which was well established causally, came out of control trials data, there is no question about the reality of that risk.

Again, in my own personal view, I don't think the data that we have here rise to that level, to mandate a medication guide to warn patients about something which we don't even know is real yet. Again, very soon all of these labels

will have the same type of language that Adderall has, alerting clinicians to the possibility of risk in patients with underlying structural defects. But I still think that the right place to go is to do a systematic trial to try and better define the risk.

DR. GROSS: Dr. Davis?

DR. DAVIS: In looking at a two-tier approach, a long-term approach to these trials and now, I am concerned about effectively informing the physician and the parent or the patient, and I don't think that for the parent a handout alone will do it. This has important information in it but part of what they want is the information from the physician and probably the pharmacist. Right now, I don't know--I mean, I know you can't speak for every doctor that prescribes these medications but I don't know how much communication is taking place before prescriptions are written, sitting down with the child and the parent to discuss these things to adequately inform them.

DR. GROSS: Dr. Moore?

DR. MOORE: I think when considering this issue that we are talking about, maybe adding a black box warning, we have to remember that in children many times these underlying structural heart conditions are undiagnosed and therein lies a lot of the difficulty. We have a large population conceivably that would benefit from use of these medications and there is a small number of patients who are below the radar as far as having structural heart disease. One of the persons testifying earlier mentioned a child with hypertrophic cardiomyopathy undiagnosed. Unfortunately, that is the problem and I think a lot of the practitioners who are prescribing these medications are doing a physical exam, maybe an electrocardiogram, but this really isn't adequate screening to identify those rare structural heart disease patients who are children who may be at increased risk here. I think that is the essence of the problem. It is a very difficult one.

DR. GROSS: It is difficult; that is why we are here. Dr. Stemhagen?

DR. STEMHAGEN: I would just like to make a comment to echo what Dr. Laughren has said. It seems to me that the evidence that we have been given today, and a lot of discussion, has been about potential signals from spontaneous reports and we are sort of leaping to a conclusion without thoroughly understanding a lot of the limitations of those things, a lot of the confounders, and we are being asked about potential studies to look at those things and, all of a sudden, we are now leaping to black boxes. I would just like to take a step back and sort of ask everybody to look at the evidence that we might have first.

DR. GROSS: Dr. D'Agostino?

DR. D'AGOSTINO: This discussion is very important because I think what is sitting on my mind is the seriousness and the ethical issues in some of the options that are given to us. We are talking about large simple trials that will take years to put together and run, and so forth. My sense from some of the presentations is that we should sort of be focusing on retrospective studies

because, with the feasibility type discussions that we had, we may have in the databases enough information to reach a conclusion, and so forth. As a sort of originally mathematical statistician, I could go on all day talking about all the different options and designs, and what-have-you but what I would like to sort of put before the table is the seriousness of making these different options.

I would say a large simple trial was ideal but I am not so sure, given the issues--the ethical issues and what we think about the drug, that is the best way to go and I want to make sure that we sort of get that on the table as we discuss these different designs, what is the seriousness and what are the ethical issues that are involved with the suggestions and what is the best way of getting the data.

DR. GROSS: Dr. Rappley has a comment.

DR. RAPPLEY: I think there is a lot of improvement that we could make down the middle in this discussion in the sense of the general

practice of medicine and pediatrics or care of children with this disorder. Perhaps through the specialty organizations we could--perhaps it is not the purview of the FDA or perhaps it is--make recommendations for the short term about the intervals at which children should be monitored; about the need to check blood pressure and pulse at each of these visits; about the need for auscultation of the chest. These are very simple measures and we know from our claims data that there is a high degree of variability in how children are monitored once they begin to receive these medications.

So, I think there are big questions--whether or not this deserves a higher level or warning; whether or not we should institute comprehensive screening programs and periodic assessment with expensive cardiac diagnostic procedures. Those I think can be addressed as we look at the long-term studies but short term there are some very simple things we can do, like check with our patients every few months,

every three to four months as a recommendation coming out of most of our organizations and make sure that that includes the very simple measures of heart rate, blood pressure, height, weight, indications of side effects, indications of effectiveness. Going back to the basic principles of good medical practice I think we have things we could gain in both addressing the problem and furthering our understanding of the problem. For example, as we come online with EMR systems that are very widespread, and creating national databases, if we, indeed, could track blood pressure and pulse, height and weight over long periods of time with children who remain in our practices we could begin to answer these questions. Thank you.

DR. GROSS: Art Levin and then Stephanie Crawford.

DR. LEVIN: I just want to return to something that Curt mentioned because the more I thought about it, the more I think it is sort of an ethical imperative on the part of the agency. That

is, how do we apprise the public of uncertainty? You know, in this day and age, I don't think it is satisfactory to say we don't have sufficient evidence to be able to say that. I think we have to recognize that when a drug is approved and marketed the public assumes a level of comfort in the safety of that drug unless they are told otherwise. And, for us to sit around and talk about this, to have three advisory committee meetings discussing the signals and not to make, at the very least, a very strong warning to people that there is uncertainty here about the safety of these drugs and that they need to be aware of that pending clarification I just think is inappropriate, unethical behavior.

DR. GROSS: Dr. Crawford?

DR. CRAWFORD: Thank you. I would just raise a question. As we are considering these questions are we only to consider the use of these drugs in ADHD? Another labeled indication both for amphetamines and methylphenidate is narcolepsy, though for a much smaller number of the population

and, certainly for the amphetamines, though it is not labeled and not generally recommended, we know that they are sometimes used for appetite suppression. So, especially with the labeled indications, are we only to consider them in terms of ADHD and not consider that they are also used for narcolepsy?

DR. GROSS: Steve?

DR. NISSEN: Let me say where I think the rubber meets the road here. If the current warnings were adequate we wouldn't have 2.5 million children and 1.5 million adults taking these drugs. I mean, it is just self-evident to me that the exponential growth in the use of the drugs suggests that the public and practitioners are unaware that there are people sitting around this table that have a serious concern about the safety.

Now, why do I think that there is less uncertainty than some others? How are these drugs different from Ephedra? How are they different from phenylpropanolamine? Again to quote Bob Temple, we have priors here. We know that giving

drugs like this to adults has been associated with serious consequences, serious enough that the agency has taken some pretty decisive actions. So, we are going to take drugs that are chemically very closely related, that have the same kind of physiological effects and we are going to give them to three or four million Americans without putting a black box on?

I think Arthur is right. I mean, to me, we have to elevate the level of concern and if it slows the growth of this, that is probably appropriate because I think most observers would argue that ten percent of ten year-olds do not have this disease and what has happened is that this is out-of-control use of drugs that have profound cardiovascular effects and, as a cardiologist, I can tell you that.

I can also tell this committee that there is an animal model for dilated cardiomyopathy. What you do is you give animals amphetamines chronically and they develop fibrosis and they dilate up and they develop cardiomyopathy. We know

a lot about what happens when you give sympathomimetic drugs to human beings. And now that we are giving them to a large number of adults we have a potential public health crisis here, and I think that this committee--I mean, we can say, all right, we will do these large-scale studies and we can kind of academically discuss it but I think patients, families and parents need to be made aware of the concerns.

DR. GROSS: I have a question for FDA. Was the data any better for troglitazone and some of the quinolones that were withdrawn? Was the data any better? Deaths were caused. Was the data any better so that those drugs should be withdrawn?

DR. TEMPLE: Let me just be sure everybody knows what we did with PPA and Ephedra. PPA was withdrawn because a retrospective study found evidence of stroke early after taking it, bleeding stroke, hemorrhagic stroke. Nothing else. No heart attacks. You know, you might wonder why it didn't do those but that is the only thing that was ever found.

For Ephedra, which I had a lot of to do with writing, what we said was that for a drug that hasn't been shown to do anything, the fact that it has these properties of being bad for you if you have heart failure, of increasing your heart rate and increasing your blood pressure are unacceptable. We made it crystal-clear that if anybody showed that the drug had value that would be a whole different argument.

So, remember that you just heard this drug has value. It was very hard to find evidence that Ephedra actually did these things. We did what you said. We said our prior applies when there is no evidence of benefit.

For troglitazone, which I remember very well, it should be remembered that we did not remove that drug from the market until two alternatives that did not have liver damage potential came along. We waited. We watched. We met every week or every month, whatever it was, and we waited to see that rosy [?] and pio [?] didn't seem to be hepatotoxic. The evidence that

troglitazone was hepatotoxic was simply overwhelming. There was no question. There were numerous cases of fatal and very severe liver injury that could only have been attributed to it. Dozens and dozens--David Graham probably knows--but well over a hundred.

So, those were very clear. The drugs that have been removed because they caused torsade caused a very unusual effect and they all prolonged the QT and the evidence was overwhelming. I think the message that Tom was giving is that it is hard to look at the evidence that we have seen to date and say that we know the answer. Now, that is not to say that amphetamine-like drugs shouldn't raise your ears. That is sort of why we are coming here to figure out how we can find out about it.

I will tell you my principal worry is that in an effort to design the study that will have enough events we won't design a study that will find the events we are really worried about which, to me, is sudden death. It isn't so much acute coronary syndrome because that is a totally

different thing; that is progression of underlying disease. That is my worry. Anyway, I hope that answered stuff.

DR. GROSS: The deaths that were clearly due to troglitazone, you mentioned there were a dozen or a couple of dozen--

DR. TEMPLE: No, many more.

DR. GROSS: Many more?

DR. TEMPLE: Yes.

DR. GROSS: Have there been that many deaths associated with these sympathomimetics that you feel comfortable saying are clearly associated with them? I know that for a lot of deaths the data was very mushy and you couldn't be sure, but can you extract from the deaths that occurred evidence that many of them were clearly associated?

DR. TEMPLE: Well, other people have to describe that. I went over the first 12 deaths initially associated with Adderall and, you know, when somebody dies suddenly you don't know what to make of it. A couple of the deaths were bizarre--a kid left in the hot sun for hours and hours. Those

you wouldn't attribute to the drug. But some of them were just people who died suddenly, often in association with considerable exercise and you had no way of knowing whether the drug was responsible or not. What our analysis focused on is what is the background rate of this in those populations and there are various estimates. The conclusion that we reached at the time was that it was not clear, even taking account of under-reporting, that the rate of these events was more than you would expect in that population. Those are always highly debatable judgments obviously, but that was the conclusion that was reached for both Adderall, which we were focusing on, and methylphenidate and at the time we had about seven of these. I gather there are some more.

So, there is no way to say in the case of sudden death whether the drug was responsible or not. So, it is always possible that they were and we did our best shot at estimating what the rate was. But those efforts are always unsatisfactory, which is really why we are here to see if there is

a better way to do it.

For troglitazone, by the way, those were not all the deaths. Those were people with diabetes. There were thousands of other deaths I am sure. These were the hepatic deaths that there were hundreds of.

DR. GROSS: Sean?

DR. HENNESSY: It is almost as if the spontaneous reports are peripheral to the issue. If we were sitting down and thinking about giving amphetamines and amphetamine-like drugs to large numbers of people for an indication that is not life-saving, giving them even in the absence of spontaneous reports, I think most people would be comfortable with stronger warnings on the drugs than we have now, apart from the spontaneous reports.

DR. GROSS: Other comments before we get to the questions? Tom?

DR. FLEMING: I am struggling, not with the issue that there is clear evidence that needs to be addressed, I am struggling with getting a

sense of what the magnitude of this effect is in the context of what several have already said appropriately--issues of benefit to risk. Robyn was making that key point earlier on and Sean made the point that when we look at relative risk we also need to look at the background rates. As Steve and others have clearly articulated, there is a preponderance of evidence here to raise serious issues that need to be addressed in a responsible way considering mechanisms, class of agents, adverse event reporting system data and preliminary analyses from large databases.

Yet, my concern is that there is huge uncertainty about what that actual effect is. If we use the adverse event reporting system data, which is just one piece of the whole picture, it might suggest that there is an increase and it would suggest that there is an increase that would be comparable in magnitude in a relative risk sense in adults and children. If you are comparing amphetamines against methylphenidate, for example, and this is shaky data but it would say there is a

relative risk maybe of 2.5. Well, a 2.5 relative risk if--a huge "if"-- if this were real in the adult setting would be translating to 150 excess cardiovascular deaths, MIs and strokes per 10,000 people. That is triple what we think the COX-2s do. For sudden death it could be 30 per 10

5.

Conversely though, in children if--if, if--that same relative risk applies as the adverse event reporting system say, when you have a background rate of sudden death of 0.3 per 10

5,

that translates into 0.4 excess deaths per 10

5,

which is 1/30 what long-acting beta agonists do for inducing asthma-related death.

So ironically, while a lot of the focus is in the children, in the pediatric setting where at least historically the use has been the greatest, there is now this emerging, very substantial increase in adults. Just looking at these data, these data suggest to me that in the pediatric setting it is highly complex. There is benefit. There is clear benefit. There is a suggestion of risk. This risk though, when you look at the

absolute numbers as Sean was saying, looking in the context of what the actual relative events would be in the control, it is a very small amount compared to what it is in adults. How do we view this? The numbers are telling me that the magnitude of the excess risk, if these 2.5 relative risks are real--I keep saying "if"--if they are real is quite profound in adults, suggesting that it would have to be an enormous benefit to offset that risk. Whereas, it is much more complicated in children where there is substantial benefit and these risks of 2.5-fold translate into very rare increased events.

So, what is our sense of how much excess risk there is, and what does that have to be to justify actions such as a black box, and do we behave similarly in adults and children?

DR. GROSS: The FDA wants us to answer their five questions. Where do you want to go with the discussion?

DR. NISSEN: You know, I know we are probably not supposed to take votes and we are

supposed to all behave and do this, but I think we are asked to give the agency advice and I didn't want our advice to be structured necessarily exclusively around the way the questions were. So, I would love it if the Chair would entertain a motion for a recommendation which would be the one that I suggested, which is that a black box is in order, and could be removed if data were to be obtained that would not implicate the drugs, and that a patient guide be developed that would warn families of the potential risk. Those two things I think would make a lot of sense and I think it would be great if we could give the agency--I am in the minority here or maybe I am not, and it would be nice to know if there is, in fact, a consensus around the table that something stronger needs to be said and, you know, we can at least feel like we have done our ethical duty here.

DR. GROSS: Okay, so you made a motion. Is there a second to the motion? Second. Any discussion?

DR. LAUGHREN: Can I just ask a question

before you vote? What language would you put in the black box?

DR. NISSEN: What I would say is that sympathomimetic drugs of this type have been associated with increases in blood pressure and heart rate which can result in heart attach, stroke and sudden death, and that there is uncertainty about the precise risk for this class of drugs but that it is an important potential risk that should be considered in prescribing them.

I mean, I can't write it off the top of my head but, you know, give me a little bit of time and I think I could fashion something which would include an understanding that this class of drugs, sympathomimetic drugs, do things to the heart that have the potential to cause harm and that other drugs in the class have been shown to cause harm, and that this should be taken into account when deciding about risk and benefit. I just think it is a way of getting their attention so that people are thinking about that.

DR. LAUGHREN: Just to be clear about your

position, it is because you seem to be much more compelled based on theory and similarity to other drugs that you believe have a real risk than the spontaneous reports for these drugs.

DR. NISSEN: Well, again, I am not very confident about the spontaneous reporting system. We know that you get 1-10 percent of the actual events reported. You don't get very much clarity and you almost never can get a very clear idea for those. But, yes, I mean, I think when you have a lot of priors--I mean, we had an advisory board panel and Bob Temple was there where we talked about blood pressure and we came to the conclusion--I believe, Tom, you were on that panel as well--where we said that drugs that decrease blood pressure decrease cardiovascular risk and drugs that increase blood pressure should be assumed to increase cardiovascular risk. I mean, we made a very clear statement, which was I think accepted by the agency, that it is not a good thing to give vasoconstrictor drugs and drugs that increase heart rate. So, we have a lot of priors

here about this type of situation. We do have the phenylpropanolamine and Ephedra story. I am recognizing there are benefits but I think the fact that amphetamines would increase cardiovascular risk by increasing blood pressure and heart rate is just not rocket science. I mean, I think it is kind of self-evident and I think we need to tell people because the message isn't out there given the enormous increase in use of the drugs particularly among adults.

DR. GROSS: Sean?

DR. HENNESSY: I think we also need to be careful about dialing up messages in the black box territory particularly in the face of uncertainty. The analogy I draw is to drug-drug interaction warnings that come across so frequently that they get ignored. I feel comfortable saying that there should be additional warnings. I am not sure whether it should be a black box or not. So, I guess I would ask the person who made the motion if they would accept a friendly amendment to the motion to remove that it necessarily be a black box

and let that decision be made by the agency.

DR. NISSEN: Well, the agency is ultimately going to make its own mind up. We are just advisory and we know that we are just advisory. What I was really trying to accomplish is to elevate the warning high enough to make people think twice before they give the drugs to an adult with symptoms that maybe are pretty marginal. Is that good public health policy? To say that before you give a 50 year-old a drug that increases heart rate and blood pressure you ought to really think pretty hard about it?

And, the only way you get people to pay attention is when you put it in a black box. It just doesn't seem to get there if you don't do something pretty dramatic, and that is why I made the motion the way I did. It is because I want to cause people's hands to tremble a little bit before they write that script, and the only way I know to do that is to get their attention with a black box. Now, that is the reality.

DR. GROSS: Last comment from Robyn. Then

we have to address the questions and maybe we will vote after we address the questions.

MS. SHAPIRO: I just want to support the notion that an appropriate additional disclosure of information, whatever that format may take, about both the safety signals and the uncertainty is appropriate. Whether or not it should include Tom's observations about the difference between adults and children, which I found fascinating, I don't know.

A critical piece, in my mind, why we need to do this, and this goes back to something Sean said earlier, is that there may be benefits, although I am still not satisfied with the discussion we have had, but this is for a non-life-threatening condition. So, the opportunity or the acceptability of being more restrictive, more paternalistic, more careful in the way that we have discussed I think is justified.

DR. GROSS: Bob Temple and then we will start with the identified questions.

DR. TEMPLE: Actually, I wanted to pursue the line that Tom was asking Steve. To say that this drug raises blood pressure and you should monitor blood pressure is a fairly straightforward thing. To say that people with heart failure or history of heart disease can be badly affected by sympathomimetic drugs--which we have many examples of and, of course, coffee is a sympathomimetic drug as we all know--that is one thing. It is quite different to say we have observations that make us particularly worried. You know, from hearing Tom, and I would endorse this too, we don't see too much in the signal, enough to pursue it, and probably the main reason for pursuing it is the very thing you are saying, that is, it is a class of drugs that you would have a prior nervousness about.

So, is what you are suggesting that there ought to be more attention to these known properties, or that there ought to be something that says we know enough to be worried because of observations? It would help to have some idea of that.

DR. NISSEN: It is a little bit of both, Bob, I think. Let me tell you what I am worried about from a public health perspective, which is really what we are all about here. We are seeing enormous growth in the use of the drugs in adults who are, in fact, the most vulnerable population here; that this diagnosis of adult ADHD could continue to exponentially grow and we could then learn five years from now that the drugs increase two-, three- or four-fold the risk of death, stroke and heart attack. We would have sat here today and not acted and regret not acting.

Now, I think that it is better to take a conservative position which says that we have a lot of reason to believe that drugs that increase heart rate and blood pressure are not good for adults, and they are probably not good for kids but they are definitely good for adults. And, we have to warn people because, if we don't, we may see a proliferation of use of these stimulants to the point where we have created a lot of public health problems that would have been prevented if we had

simply said to people you ought to be more careful with these drugs, that we have some reasons to believe there are hazards.

DR. GROSS: It sounds to me that the guidance for the parents is at least as important as the black box warning. Why don't we get over this issue? Let's just vote now and then we will go on with the questions. All those in favor of the motion, which is an advisory comment to the FDA and is clearly not binding because we are an advisory committee? We are going to have to start with Dr. Stemhagen and go around the room. Announce your name and your vote.

DR. STEMHAGEN: I am a non-voting member.

DR. GROSS: Okay, that was easy.

DR. D'AGOSTINO: Are we pushing the black box notion?

DR. GROSS: No, the black box and medication guide is the motion.

DR. D'AGOSTINO: I thought we modified it.

DR. GROSS: The wording in the black box has not been fully described. That is something

that would have to be worked out.

DR. D'AGOSTINO: Well, I am not comfortable with the black box idea. I am very comfortable with--

DR. GROSS: With the medication guide?

DR. FLEMING: Can I suggest that the FDA would find it, because we are only advisory, more helpful, rather than just saying yes/no, to give our sense of what we think should be done?

DR. D'AGOSTINO: Exactly. I will start off. I don't like the idea of the black box because I don't want a black box to sort of lose its impact by loading a lot of things in the black box. But I am very concerned that more needs to be addressed for this drug and it should be made available to the parents and to users.

DR. GROSS: If that is the case, why don't we split it into two, one black box and one medication guide? So, let's start with the medication guide.

DR. D'AGOSTINO: Yes.

DR. DAVIS: Wait. Is it only two things?

DR. GROSS: It is only two things, medication guide and black box.

DR. DAVIS: To convey concern about warnings?

DR. GROSS: Right.

DR. DAVIS: We have to limit ourselves right now to black box or medication guide?

DR. GROSS: Well, right now. I mean, if you have some suggestions, you know, later we can consider that.

DR. D'AGOSTINO: Do you want me to state my name also?

DR. GROSS: Please.

DR. D'AGOSTINO: D'Agostino, yes.

DR. GROSS: Sean?

DR. HENNESSY: We haven't talked about medication guides. I am not sure I know what a medication guide is to be able to vote on that.

DR. GROSS: So, do you want to abstain?

DR. HENNESSY: All right, I will abstain on medication guide and I will vote no on black box. Oh, we are doing one at a time, I am sorry.

So, I abstain on medication guide.

MS. SHAPIRO: Robyn Shapiro, yes on medication guide.

DR. FURBERG: Furberg, yes on medication guide.

DR. GARDNER: Gardner, yes on medication guide.

DR. NISSEN: Nissen, yes.

MS. DOKKEN: Dokken, yes.

DR. MANASSE: Manasse, yes.

DR. GOMEZ-FEIN: Gomez-Fein, yes.

DR. GROSS: Gross, yes.

DR. MOORE: Moore, yes.

DR. RAPPLEY: I don't know if I vote.

DR. GROSS: You abstain?

DR. RAPPLEY: No, I don't know if I vote? I do vote? Yes, to medication guide.

DR. DAVIS: Davis, yes to medication guide.

DR. FLEMING: Fleming, yes to medication guide and I am uncertain about black box--

DR. GROSS: We are not voting on that.

DR. CRAWFORD: Crawford, yes to medication guide because I know what they are, but I would just like to make a comment that while I do support this, in general I am somewhat uncomfortable when the committee is asked to make public votes on things we have not been given more background on and this motion is brand-new and we are being asked to vote on things we were not given background information about.

DR. GROSS: Arthur?

DR. LEVIN: Levin, yes.

DR. GROSS: Yes, are you going to vote?

DR. LAUGHREN: No, no, I am going to ask for clarification on which of the drugs that we are considering this applies to. We have been talking mostly about stimulants. There is one drug in this class, atomoxetine, which is technically not a stimulant. It doesn't even have a classification but it does have a modest effect on increasing blood pressure and heart rate.

DR. NISSEN: I think that I would make it a class type of a warning until we have more

information about relative risk, all the stimulant drugs.

DR. LEVIN: I am looking at a medication guide for Strattera. It already has a medication guide.

DR. NISSEN: Yes. Again, the sense of the motion, Peter, was that the medication guide would warn of the potential for cardiovascular risks, including some information about the preexisting structural heart disease, so that people would know if their child has been diagnosed with, you know, some form of heart disease they should be aware of the potential for increased risk and the possibility that, even in the absence of structural heart disease, the potential exists for there to be increased risk for a child or adult.

DR. TEMPLE: But it is not a sympathomimetic. You are saying all the ADHD drugs, even a benzodiazepine ought to get it?

DR. GROSS: No, I think we are saying just the stimulants.

DR. NISSEN: What I intended was the

stimulants.

DR. TEMPLE: Well, that is what Tom asked you.

DR. GROSS: Okay, so we have a medication guide recommended to the FDA for the stimulants. Now we are going to vote on the black box for the stimulants. Dr. D'Agostino?

DR. D'AGOSTINO: D'Agostino, no.

DR. HENNESSY: Hennessy, no.

MS. SHAPIRO: Shapiro, abstain.

DR. FURBERG: Furberg, yes.

DR. GARDNER: Gardner, no, with a comment. I think that the communication of uncertainty is within the FDA's new policies of transparency and trying to communicate better with the public, and I think you have systems for doing that. So, although not a black box warning, I would like to have you consider communicating more broadly the uncertainty that is being investigated through your current mechanisms.

DR. LAUGHREN: I could comment briefly. We do have a number of mechanisms. We have

something called sheets for both patients and for prescribers in which, in certain situations, we have put out information about a finding for which we don't yet have certainty. We do have a number of ways of communicating information short of making major changes to the label.

DR. NISSEN: My vote is yes, and I also would like to encourage the agency to use whatever means they have for making certain that there is increased awareness of the potential for harm here.

MS. DOKKEN: No, on the black box but I want to underscore what Dr. Gardner said about looking at other ways of communicating uncertainty.

DR. MANASSE: Manasse, yes for the black box, and I provide a yes vote because I think this is a serious issue relating to practice behavior both for pharmacists and for physicians, and I think the only way we are going to get the attention of the medical community and the pharmacy community and sharing with patients what the potential risks are with these medications is through the black box warning. DR. GOMEZ-FEIN:

Gomez-Fein, yes, I agree with the black box warning. I am also concerned with the over-prescribing of these medications and I don't believe everybody knows the extent of the effects as we have been describing here and I think that we need to alert the public and the medical community of these concerns.

DR. GROSS: Gross, I am a little bit equivocal on the black box but since I have to vote one way or the other, I will say yes, with the understanding that it is made clear in the black box that the data is only suggestive at this point but, because of the gravity of the side effect, namely sudden death, the physician needs to be made clearly aware of that concern.

DR. MOORE: Moore, I will vote for the black box but I also think there need to be some qualifications. I think it should specify that with regard to children the unknown risk may lie mainly in children who have undiagnosed structural heart disease or the tendency toward arrhythmia disorders; that it does not appear so much to be in

just the general population. Whereas, in the adults the risk seems to be more in patients who have possible comorbid conditions such as hypertension, which is quite prevalent. I do think we want to be careful not to stunt the tremendous benefit that can occur in the pediatric population from these drugs.

DR. RAPPLEY: Rappley, no on the black box because I don't feel that we have demonstrated risk that would justify a black box warning, and I think that we have another mechanism to convey the uncertainty around the issue. I also feel a bit uncomfortable that we are confusing our concern about indiscriminate prescribing and casual diagnosis with risk of medication, and sort of leveraging the mechanism of the FDA to convey a message that perhaps should be strong and clear but come from something other than a black box warning. Thank you.

DR. DAVIS: Davis, I too have very mixed feelings about the black box. I am voting yes, but my desire is to effectively communicate with the

prescriber who can have discussions with parents and with adults about the uncertainty and the risk, and I don't know if the black box and the medication guide effectively does that. People trust their prescriber and their physician, and that is where that communication really needs to take place, but I don't know what the FDA can do about that exactly.

DR. FLEMING: I am unclear about whether there should be a black box, largely because of the uncertainty I have about the magnitude of the risk, yet I am very persuaded that if the FDA is not going to use a black box there needs to be an approach that will effectively allow patients, parents and caregivers to be clearly informed, much in the spirit of what Dr. Gardner was advocating. So, if I could be persuaded that that could be done effectively without a black box, then under those conditions I would be accepting of not having a black box. If not, then there would need to be a black box but I am believing that there will be alternatives that could be pursued.

DR. GROSS: Stephanie?

DR. CRAWFORD: Crawford, for right now I am voting no on the black box, the reason being that there have been differing opinions expressed around our table as to what the language would be to go into that black box. So, I am a little uncomfortable at this point to vote yes without knowing that precise language.

DR. GROSS: Last but not least?

DR. LEVIN: Levin, yes on the black box, and reminding everyone that when there is a black box warning that also appears at the top of the medication guide, which I think is important. So, it is both to the prescriber and to the patient/family of the patient who will get the warning.

Just as an aside, I think we know that it is very difficult to change prescribing behavior and, unfortunately, I think we may have to act in these sort of heavy-handed ways in order to get people to pay attention. I have defended, for example, official prescription forms in New York

State for that reason. It is sort of interesting that in the geographic distribution for the use of Ritalin, New York State is at the second lowest level and in New York State it requires an official prescription which, as Steve said, makes physicians think about things when they are writing a prescription that they might not if there wasn't a black box warning.

DR. RAPPLEY: Well, that didn't work in Michigan. We were in the top five for decades.

DR. GROSS: Thank you, all. Now we really are moving on to the questions. Please identify and discuss the most important outcomes to study in both children and adults. Consider outcomes based on differences in age groups; how to validate the outcomes; and who the comparison group should be. Who wants to go first, or are you all worn out by this? Yes, Dr. D'Agostino?

DR. D'AGOSTINO: I will start it only to be contradicted later, but I think in the children the sudden death is the most--

DR. GROSS: Let's stick to the questions.

DR. D'AGOSTINO: Isn't that children with choice of outcomes?

DR. GROSS: Yes.

DR. D'AGOSTINO: So, I am saying in the children I think it is sudden death. In the adults I think it is the full cardiovascular--MI, the stroke and the deaths as the primary outcome. I think also even in the children the MIs and the strokes need to be considered very seriously. Do we want to talk about validation? Do you want to go down the three?

DR. GROSS: Sure, please.

DR. D'AGOSTINO: I think it is imperative that, whether it is retrospective or not, there be adjudication of the outcomes; that they are validated. Also, obviously, death also should be looked at. For the comparison group I think you need a general population but you also need some kind of a consideration of children with this condition who are not on the drug. Let's say they have attention deficit and they don't take the drug, versus they have it and they do take the

drug, I think you need that as a comparison also in setting up of these different trials.

DR. GROSS: I am sorry, could you say that again about the comparison?

DR. D'AGOSTINO: In the comparison group I think you need a general population so what is the background rate, but I think also as you focus on what is the effect of the drug--I don't know if there is something biologic that is going on with the children that have this diagnosis. It seems to be just a clinical judgment in terms of manifestation of activities, and so forth, but if there is something biological it would lead me to say that in addition to a general population or background rate you need to have a sense of what would happen to children with the attention deficit who aren't taking the drugs. So, there would be two comparison groups for consideration. Is that all right?

DR. GROSS: That is fine. The votes have been tallied, for your information. The medication guide, 15 yes; 1 abstention. The black box, 8 yes;

7 no; 1 abstention. Thank you, all. Any other comments? How about for a comparison group, ADHD children not treated? Sean?

DR. HENNESSY: While that would be an ideal group to study theoretically, I think practically it is going to be difficult to identify. I think mainly the diagnosis is used as a rationale to prescribe the drug and that the number of children with the diagnosis without the drug is likely to be vanishingly small. That doesn't immediately lead to another comparison group.

Let me just throw this out. I haven't thought through it very much so let me back up for a second. In administrative claims databases in particular it is often difficult to distinguish absence of claims to figure out whether that means the child was healthy or whether you lost information on that child, or maybe they were in a managed care plan, etc. One way around that is to identify another chronically used medication to use as a control group. Of course, in this case it

would need to be a chronically used medication that we didn't think was associated with the outcomes of interest and was used as treatment for a disease that we didn't think was associated with the outcomes of interest. For example, asthma inhalers would not be a good choice because the disease and the treatment may be associated with the outcome. I am thinking that maybe treatment for seasonal allergic rhinitis might be a good choice but, again, that might be associated with asthma. So, if there were some chronically administered medication that wasn't associated with sudden cardiac death and used to treat a condition that is not associated with sudden cardiac death, that might be another potential control group.

DR. GROSS: Can we get some help from the pediatricians here as to what drugs might be good for a comparison group for chronic illnesses in children?

DR. RAPPLEY: Asthma would be the other condition that affects a very large number of children, especially school age children. You

could possibly look at amoxicillin, often noted to be a pediatrician's friend and a medication frequently used. But that is kind of a different category altogether in that it is not chronic use.

DR. GROSS: Is amoxicillin used chronically? No?

DR. RAPPLEY: No.

DR. GROSS: How about steroids for JRA?

DR. RAPPLEY: No, the steroids have so many other confounding complications that I don't think that would be appropriate.

DR. GROSS: Okay. Any other drugs or patient groups you could recommend?

DR. RAPPLEY: I will think about it.

DR. GROSS: Good. Dr. Stemhagen?

DR. STEMHAGEN: A comment on the comparison group from the NIMH study. It sounded like there was a cohort of patients who were on behavioral therapy. So, as long as it is not a carve-out within that managed care population, there could be another group of patients who do have the diagnosis who are not on some kind of

medication. The question, of course, is how different are they; what selection bias, but that is a concern with observational studies anyway.

DR. GROSS: Curt?

DR. FURBERG: In terms of outcome, because of the small numbers and the fact that there is a common underlying mechanism behind sudden death, MI and stroke, I would like to see those combined, particularly in kids, to get the numbers up. And, I don't think we should throw out some of the data that David showed. Kids hospitalized for arrhythmias and hypertension, I mean, as a primary diagnosis for hospitalization, that is fairly severe. At least include them as secondary outcomes.

DR. GROSS: Any other comments? I know there are always going to be some comments. Yes, Tom?

DR. FLEMING: I largely agree with Ralph's formulation of the endpoint. I guess I would say in both settings, pediatric and adult, I would be interested in cardiovascular death, stroke and MI

as an endpoint and sudden death as an endpoint. Technically, I would also be interested in overall mortality because I always worry that we are not including certain unintended mechanisms beyond those that we are capturing with cardiovascular and, yet, I realize that we can greatly dilute our estimates in the setting. So, I would agree that cardiovascular death, stroke, MI and sudden death would be two endpoints I would go after. Validation, to me, is more important in those settings where the assessments are made where there is open label, i.e., where people know what the intervention is.

When it comes to selection of a comparison group, a comment that I will be making later on is that I believe it is feasible and important to do a randomized trial in adults. In the pediatric setting I think it is not. So, the discussion that we have had on the choice of the control group largely relates to the pediatric setting and these comments are relevant to the struggle. But the principle that I think is important is that the

control group needs to be an ethical standard of care, an appropriate standard of care, but ideally one that is thought to have a relatively small effect on what it is you are trying to assess here. If we are trying to rule out the safety issue of cardiovascular death, stroke and MI, then ideally we need to try to strive for an appropriate standard of care that likely wouldn't increase.

In the adult setting I think this is achievable. There is an increasing use of this class of agents and, yet, with the tremendous concern about what a two- or three-fold increase would mean in terms of cardiovascular death and MI there surely would be equipoise here, and randomizing people for a year to agents in this class versus non-agents should be very doable. In the pediatric setting though such a trial wouldn't be achievable or wouldn't be feasible.

DR. GROSS: Dr. Rappley?

DR. RAPPLEY: Because later, in the design section, I was going to suggest that we will need complementary designs, one of them being some form

of chart abstraction, I think it is important to examine the relationship of increases in blood pressure and pulse and exercise in young people, children and adults, and extreme exercise as well, and also look at this notion of duration of treatment and the cumulative effect on the simple parameters of blood pressure and pulse.

DR. GROSS: Any other comments on the first question before we go to the second? Sean?

DR. HENNESSY: I wanted to endorse David Graham's suggestion for using unexposed person-time in exposed people as another potential control group, either directly or in the context of the case crossover study.

My second comment is that I am not sure what I would do with a study that included as a single outcome both hemorrhagic stroke and thrombotic events like MI and ischemic stroke.

DR. GROSS: If there are no more comments on question one, let's go to number two. That reads, please comment on whether ADHD drugs should be studied individually or collectively as a class.

Remember that not all of them in the stimulant class. Sean?

DR. HENNESSY: The null hypothesis would be that all the amphetamine-like drugs have the same effect until proven otherwise so, to the extent that individual drugs can be looked at, they should be. But when you run out of numbers, as you will, lumping is going to be necessary and I would assume that the drugs are different until proven otherwise rather than the other way around--I am sorry, assume that the amphetamine-like drugs are the same until proven otherwise rather than the other way around.

DR. GROSS: Ralph?

DR. D'AGOSTINO: If we go for the collective use, I can see what will happen. We will end up with a study where there will be a mix of all different drugs and then we will say, well, gee, we are not really certain that drug A is like drug B, is like drug C, and we will start splitting it out and we won't have any conclusions. So, I would say that we should be trying to look at them

individually and understand what is going on with some of them. Then we can start making inferences about the class as opposed to the class first.

DR. GROSS: Steve?

DR. NISSEN: Yes, it is going to come up again under question three but I just want to raise for people's awareness the possibility that one of the things to be done would be to do a shorter-term study looking at things like ambulatory blood pressure and other kinds of monitoring to try to understand whether there are major physiological differences between the drugs. Then, based upon that, it would let you at least get some idea if they were more similar or dissimilar. For example, if you saw that amphetamines had twice as much blood pressure and heart rate increases as methylphenidate or the other agents, then you would have some further basis on which to make that decision. I actually think some of those things are pretty easy and pretty inexpensive to do, and I will raise that again when we come to number three.

DR. GROSS: So, in the short term see

whether or not they are similar physiologically. That would be pretty simple and inexpensive to do. Tom?

DR. FLEMING: I endorse that. The notes that I had made were very similar, and that is do we have the ability in the shorter term to collect clues that are establishing not proof but plausibility of similarity. What I noted there was to go to factors such as risk factors such as blood pressure and heart rate, or using the more readily available adverse event reporting system data or observational data classifications to see whether or not there is a suggestion. As unreliable as it is, the AERS database is suggesting a 2.5-fold higher rate with the amphetamines compared with the methylphenidate--not reliable but at least suggested there. Are data such as those available, as well as information on heart rate, blood pressure or other factors that would give us clues? We could then use those clues to determine how finely we would have to address the issue. Is it a class effect alone or are there subclasses that are

generating particularly high risk?

DR. GROSS: Actually, I think some of that information was in the handouts we got. I just don't remember whether it was by class or by drug. Anybody here remember? Gerald?

DR. DAL PAN: I think Dr. Gelperin can answer that. She reported the results of some studies about the blood pressure.

DR. GELPERIN: Are you asking about the reporting rates or the blood pressure changes?

DR. GROSS: Blood pressure and pulse changes.

DR. GELPERIN: I don't think that we could comment meaningfully. I don't think that the right study has been done on that. In the children, the ambulatory blood pressure monitoring studies were small and they were done with kids on their usual drugs so the methylphenidate and amphetamine were looked at as the active, and then the control was placebo.

DR. GROSS: Thank you. Any other comments on question number two? Yes, Dr. Rappley?

DR. RAPPLEY: Maybe I am stating the obvious but I think that atomoxetine should also be included, so not just to focus on the other stimulants.

DR. GROSS: Any other comments on number two?

DR. GELPERIN: Shall I comment on atomoxetine?

DR. GROSS: Sure.

DR. GELPERIN: That actually is well described in the atomoxetine package insert. Although it is not compared with methylphenidate or amphetamine, the changes in blood pressure and heart rate as mean changes versus placebo in clinical trials are actually currently clearly described in the package labeling.

DR. GROSS: Good. Thank you. Question number three, which of the following approaches seems best to study cardiovascular outcomes with ADHD drugs? Please consider methodological issues; the nature of the outcomes; time needed to conduct the study; and cost issues for the following types

of studies, prospective case-control study, versus case-control or cohort study within a claims database, large simple trial or others that you might suggest. Sean?

DR. HENNESSY: I would recommend against a prospective case-control study because those generally need to rely on random digit dialing to identify population controls, and lots of people have cell phones these days and lots of people don't answer the phone, and there are lots of problems with identifying valid controls in random dialing case-control studies that the hemorrhagic stroke project encountered. I think that both large simple trials and either case-control studies--I am sorry, either cohort studies or case-control studies nested within large administrative databases would both be appropriate.

DR. GROSS: Tom?

DR. FLEMING: I think this is a very important question, a very challenging and difficult question and I have several thoughts I wanted to share on this one in particular. To

simplify a little bit, I am going to lump observational studies together and compare them to randomized trials although, certainly, my general sense is that a more prospective active surveillance approach is going to be more effective than a passive surveillance approach. An observational study has the advantage that it provides a more timely insight, and it is going to give fairly reliable information about issues of excess risk in settings where relative risks are large and effects are relatively rapid.

The concerns that I would have are that there are several features of a randomized trial that allow us to get a much more informative and interpretable result than an observational study. Just to mention a few of those that have come up in discussions today, it is important to have outcome sensitivity and specificity and to be able to reliably capture all events and to reduce missingness and loss to follow-up. That is a challenge in a randomized trial. To do so effectively with observational databases is

extremely difficult, and Dr. Graham has recognized in what he was presenting, for example, that some of these challenges and some of the sources didn't even capture deaths.

A second critical issue is adherence. In a setting where the goal is to allow you to rule out unacceptable risks with an intervention, having adequate adherence to that intervention is going to be imperative in order for that to be useful information. As Dr. Graham had pointed out, there is uncertainty about exposure, duration of use and use of ancillary agents in these observational databases.

A third issue is the importance of an intention-to-treat cohort to have an unbiased, interpretable result, basically having a time-zero cohort. What we want to look at is what is the relative effect of a regimen that would use one of these interventions versus a regimen that doesn't. It is not necessarily just while you are on the intervention where the outcome or effects could occur. So, how do you create a time-zero cohort

from an observational database? Steve has pointed out that for stroke maybe it would be okay to look at what is the rate while you are on the intervention versus while you are off. But for other endpoints such as MIs that would be very misleading, to attribute the events while you are off to non-treatment and while you are on to treatment. So, the principle of a randomized trial with intention-to-treat is if you want to know the one-year rate you include the one-year rate on all people, even someone who only takes therapy for nine months. It is very difficult to replicate that important time-zero cohort feature in a noon-randomized trial.

Finally, and maybe most importantly, the randomization is giving us comparability. At least, it is eliminating the systematic occurrence of imbalance. People don't use these agents at random. They clearly are using them based on specific insights. Maybe those insights aren't fully informative about whether this will be a favorable benefit/risk to them, but they are still

using judgments as to whether or not this intervention should be used. Of course, we can address this. We have covariates. We can recognize differences. But we always say the known and recorded covariates are the tip of the iceberg that explain how I am different from you, and to think that we can use those to address fully the differences has been repeatedly shown to be not true.

Now, that doesn't mean that observational studies don't serve an important purpose. They are very useful for hypothesis generation, particularly since they give us timely results. They give us clues about when to do a randomized trial and, in fact, if a randomized trial is not feasible these are the clues or the best we can do. As I said, they provide reliable insights in settings when the relative risk is large and the effects are relatively rapid. An example would be rotovirus. Another example would be Tysabri and PML. PML is a one in a million case. There is a 100 to a 1,000-fold increase even though there are only a

few events. The fact of the matter is they are events that are occurring when none should have occurred. An observational database allows us to make that inference.

Randomized trials, however, become critical in settings where a modest relative risk increase is important but the rate of that event isn't negligible. A couple of examples, with COX-2s there is a background rate of 100 death MI strokes per 10,000 people and the relative risk appears to be about 1.5. That is not a setting that lends itself well to doing an observational study. The bias that could exist from selectivity could readily overwhelm the signal.

I have more comments. Should I keep going? The bias in that setting could readily overwhelm the signal but it is a signal that we shouldn't miss because if you have a relative risk of 1.5 when you have 100 cardiovascular deaths, strokes and MIs with COX-2s, that is an excess of 50 events per 10,000 people. In the mortality setting, in fact, in the COX-2s what has happened

is that there have been randomized trials of about 50,000 people right now that have given us these insights, and there is a planned precision trial now that is going to take place that involves another 14,000 people for pair-wise comparison to more clearly understand what the actual effect is and, in particular, to distinguish between the effect of different agents in the class.

An example in the mortality setting is asthma-related deaths with long-acting beta agonists. There is a setting where the event rate is 5 per 10,000 and the relative risk is about 4. The SMART trial involved the randomization of 26,000 people in order to be able to get a more reliable sense of what that excess risk is, a risk that appears to be about 15 induced-asthma related deaths for every 10,000 people.

So, in settings where you have important effects but there are modest relative risks in the backdrop where you have a non-rare event, then the randomized trial becomes a very important tool to get a reliable sense. So, my final question or my

final comment is what does this tell us then about this class of agents? My sense is that the answer is different in adults versus children, in the pediatric setting versus the adult setting. In the adult setting, if we viewed that a 2.5-fold increase which, although unreliable, is what the adverse event reporting system data might tell us could be very plausible here, and it tells us that that relative risk rate seems to be about the same in adults and pediatric--maybe unreliable data but that is what we have before us. When you have a cardiovascular death, stroke and MI rate that is in the neighborhood or 100 per 10,000 a 2.5-fold increase is 150 events. That is an enormous number of events. Even a 1.5-fold increase would be important to detect.

But is that doable? David Graham referred to this today. In essence, the way you understand the size of a trial isn't number of patients; it is the number of events that you need. If you want to rule out a 50 percent relative increase, it takes about 250 events. To rule out a doubling, it takes

88 events. So, a 1.5-fold increase here would be 50 additional events. That is the concern we have with COX-2s. It would be important to understand that. It takes 250 events. That would take a trial of about 7,000 or 8,000 people per arm. That same study would allow us to have 50 events in sudden death according to the rates of events here. That would allow us to rule out the induction of 20 additional sudden deaths per 10,000 people.

It seems to me that it is important to have that level of insight. That level of insight, as I say, could be obtained with a study of 16,000 people, a study that is no larger than what has been expected with zaprasidone because of its effects on QTc, with long-acting beta agonists with the SMART trial, with what has happened with the COX-2s. For these types of risks it is important to have an understanding. I think it is feasible to do a trial in adults, and it is important because of the enormity of the importance of the increase because of the high background rate.

In contrast, the background rate in the

pediatric setting is one-fiftieth to one-eightieth, and if the relative risk is the same in pediatrics as in adults, then take that number that I said for an adult trial and multiply it by 50-80 and you have something approaching what David Graham said about a study that would be approaching a million people. That is not achievable. We are not going to be able to do a randomized trial to address this issue in the pediatric setting.

The only thing that is a bit reassuring about that is that in the pediatric setting when you have a doubling or even a 2.5-fold increase, you are talking about 0.4 additional events per

10 5. As I mentioned earlier, that is one-thirtieth

the rate of long-acting beta agonists inducing asthma-related deaths in the asthma population, and that is an agent that still has potentially favorable benefit/risk profile, depending on your judgment of benefit.

So clearly, as people have said, in the pediatric setting these risks need to be understood as best possible, but the substantial upside

benefit is one that also weighs very heavily here. So, I would argue that in the pediatric setting we need to do an observational study, as has been discussed, to complement what I would hope would be a randomized trial in the adult setting. That observational study could give us a sense about excess risk--it could give us clues. It could also give us better clues as to whether the relative risks are about the same in the pediatric and adult setting. Then, with the adult randomized trial, we would have the foundation to make a more informed judgment collectively, in the end arriving collectively with these sources of data to the best possible information we could to inform patients, adults, and patients and their parents in the pediatric setting about what benefit/risk truly is.

DR. GROSS: Well, Tom, you said a lot of things. Maybe what would be most helpful is if you would go home and dictate that and send it around to all of us and the FDA. We would be interested in having a chance to look it over and think about it. Thank you.

DR. FLEMING: I only said half of what I had written down.

DR. GROSS: I am sure of that. Curt?

DR. FURBERG: I agree with Tom's tutorial, but I take somewhat of an issue with the idea of a trial in the adult setting. I mean, you gave good reason for a trial but there are ethical issues. If you do a study in adults, particularly those with any cardiac condition, there is increased risk of suffering a heart attack, stroke or dying suddenly. To use your numbers, a 2.5-fold increase--how would you write the informed consent? How many people in this room would sign up for a trial where the informed consent would say if you are randomized to the active treatment your risk of heart attack, stroke and sudden death may increase by 2.5? I mean, that study is not feasible ethically. I mean, that is an ethical concern that I have about your suggestion.

DR. FLEMING: Just to clarify, the numbers I was giving were actually for a 1.5-fold increase. What I stated I think was that the data indicated

that there could be a 2.5-fold increase but that would be an enormous public health impact if it were real, but even a 1.5-fold increase would be a concern. So, the design would be to distinguish whether there is a 1.5-fold increase or not. Is that ethical? Is that something that people could readily understand as equipoise? Absolutely. We are not saying there is a 1.5-fold increase. We are saying the data suggest a concern that there may readily be an increase; then, again, there may not. The goal of the trial is to find out whether there is. If there is an increase, this is a very important insight because the intervention provides other very significant benefits.

DR. FURBERG: Yes, but you have to inform potential candidates of the trial about the potential risk and, to use your words, that could be a 2.5-fold increase. That is alarming. I would never sign up for your trial.

DR. GROSS: Ralph?

DR. D'AGOSTINO: Earlier in the discussion I raised the seriousness and the ethical issues,

and I am glad we are coming back to them. I mean, there is no way out of a large simple trial as being sort of the ideal thing, but I do have concerns. I mean, I endorse what Tom is saying a hundred percent but I do have concerns as you put that together with the issues that Curt is talking about. When I start thinking of how risk can magnify as you start increasing the risk factors if you already have a cardiovascular event--you know, the number Tom is putting forth may be an average number. It may be in some sub populations tremendously large. So, while I would endorse what Tom is saying, I think that it needs a lot of discussion in terms of its feasibility and the ethical and--when I say seriousness I mean in terms of we can talk theoretically is it a serious contended on the table, and I think that message should get across.

As far as the other, the prospective case-control study, we make our reputation in Framingham by taking relative risk of 4 and showing them really they are like 1.2 when you look at a

cohort type of study. So, as you put together these alternative studies, these case-control and cohort studies in a claims database I think we definitely should endorse, not necessarily as the best, the effort that has been going on in terms of the feasibility studies, and so forth. That looks really promising and if they can adjudicate their events and they can apply good controls, and what-have-you, as Tom points out it is probably the only thing that we should do in the children. So, I certainly would think that that should get our sort of vote of confidence.

Again, to summarize, I think the large simple trial is clearly the best theoretically. I am tremendously concerned about the ethical issues that come up with the high risk, and I think as a way of moving us into getting some answers the case-control on claims databases seems to be feasible and I think will produce good answers.

DR. GROSS: We have mentioned large simple trial a number of times. Would you define it?

DR. D'AGOSTINO: A large simple trial, in

my definition, basically would be a randomized, controlled trial where you are just allocating people by randomization to treatment A versus treatment B. What treatment A would be in this particular case would be one of the stimulants and then treatment B would have to be discussed and laid out, would it be another medication or would it be some other control, some other treatment for the individual? That would be another issue, what is the control group. Then you just follow those individuals. You keep track of their visits. You keep track of the events they develop. Again, with a large simple, as a rule you pick big things for outcomes, mortality, cardiovascular events, not things that you have to monitor heavily. We want to start looking at blood pressure and monitor blood pressure, and that would actually sort of hurt the idea of a large simple trial if you have to keep bringing them in and monitor all those activities.

DR. GROSS: And we are mentioning case-control trials as if we know exactly what we

have in mind. What are our control groups going to be, and by how many variables are we going to match them with the cases? Are we going to use one variable, two, three?

DR. D'AGOSTINO: This is where Framingham takes a relative risk of 4 or an odds ratio of 4 and shows it is like 1.2. When we start taking the case-control studies that would have very unique populations, Alzheimer's disease and so forth, everybody gets in the case-control. In Framingham the relative risk is like 1.5 or something like that because we have that whole population. And, all those issues have to be faced. What are the controls is not going to be easy. Earlier one of the presenters had a slide with propensity scores. That is a possibility. And, there was a D'Agostino on the bottom. In the case of our trying to have full disclosure, that D'Agostino is my son; it is not me who wrote that paper. But I still endorse propensity scores and that type of mechanism. But they are not easy studies. The point is that we have a database and we have a number of databases

and they have I think very good quality. I think over the years how the HMOs have improved the quality. Kaiser, for example, I think has a very good database. You can get in and get good information, but the challenge of what the control is will be extremely important.

DR. GROSS: And define propensity scores.

DR. D'AGOSTINO: Propensity scores is when you have a collection of variables. You would like to match on age. You would like to match on, say, severity of the illness. And, you have a whole bunch of contenders, possibility of variables that you could match on. There might be too many to try to set up little bins. What a propensity score does is it basically does an analysis. For those who are familiar, it sort of does like a logistic analysis where you start saying what would be the chance that a particular person could have been somebody who would have been selected for the treatment. So, you get somebody who had the treatment and you match them with a probability score, a propensity score that he or she is similar

to the one who got the treatment and you start bringing in individuals into your controls that look more and more like the actual cases, the actual individuals who got the drug in this case. If you do these, you can go back and look--you build a whole slew of variables to enter the propensity score. At the end you can actually see how well you matched, how well you balanced the whole collection of covariates between what you are calling your treatment group versus what you are calling your control group. So, it is a way of doing sort of a bigger matching without having to match variable by variable.

DR. GROSS: Gerald?

DR. DAL PAN: Yes, I was raising my hand on behalf of Dr. Temple.

DR. GROSS: Oh, Dr. Temple?

DR. TEMPLE: Thank you. I wanted to ask Tom what he thought--Ralph referred to this, what he thought an appropriate or possible control group might be for a large simple trial. All of the trials people have talked about are not in

symptomatic conditions. They are in conditions where you have it or they are active control trials. It turns out nobody believes you can do a placebo-controlled trial even in a benign condition like osteoarthritis.

I find it totally implausible that you can do a placebo-controlled trial with any great duration in ADHD. So, I think you have to come to grips with whether atomoxetine is the control and you haven't really discussed that. But that is the non-amphetamine of the group. Now, you would still have some doubts because that has never been subjected to a long-term placebo-controlled trial either, but at least you might be able to bring that off.

I also think it is worth noting that in symptomatic conditions even active control trials have a lot of trouble keeping people on therapy. The experience in the NSAID trials, for example, is that about 50 percent of people were gone by half way through. So, it is not so easy to do that.

I guess the other question I have is there

was some discussion about what the control groups might be in epidemiologic studies and I would be interested in a discussion. I find it very hard to imagine that a control group could be anything other than a group of people with ADHD on a different drug. I mean, picking people who are asthmatic, or something, that seems really scary and unlikely to tell you what you want to know. So, the details of these things are going to be important.

DR. FLEMING: Lots of issues, Bob. I agree with you that the choice of the control groups is going to be an important issue. By the way though, all of what you are saying, the choice of the right control group, keeping people on the drug, all that is equally a challenge in an observational study. It is not unique to the randomized, controlled setting that that becomes an issue.

The proper control I think is something that is going to take a lot more discussion. The way I characterized it earlier was that it should

be an appropriate standard of care that ideally would be thought to have a relatively small effect in the primary outcomes. In the adult setting it isn't clear to me that, if we made it a patient's choice, a number of people might not choose a non-ADHD intervention. We are at a time period in the adults where there is a very rapid increase in the use of these agents, which tells me that you are going through a transition period. I don't need to have everybody in the world agree to go on the randomized trial. For those people who are carefully informed about what we understand the benefits to be and what we understand the risks to be, and for those people that have equipoise we would then randomize them to one or more agents in this class against a proper control. If, in fact, we didn't think people would go on such a trial, is that because when we are telling them the truth about the risks nobody would want the agent? I don't think that is the case, but if that is why you think this would be unethical then it is unethical to not be giving a more proper informed

consent. I have always said the first time I am eligible for a randomized trial I am on that study, and I am on that study because I am going to get a better informed consent process. On average I get quality care whether or not I am on the active or the control regimen. So, this ought to be entirely ethical. I am not sure who it would be that would view it to be unethical when I give you an informed consent here and I say there is uncertainty. If you share that uncertainty you join the try. If you don't, that is fine. You are at free will to go off and either take the agents or not.

So, Bob, the bottom line is we need to decide what would be an appropriate control. I would grant you doing this in a pediatric setting would be unachievable because I think the understanding of the magnitude of benefit is quite substantial and the risks are so rare that I could believe there could be a lot of people who would elect only to take active therapy. But in an adult setting it is not so clear to me when we consider that the risks are much greater in absolute

magnitude and we are at a time period where we are emerging toward greater use, meaning that that is a time period when a lot of people aren't using these agents and a lot of people are. That lends itself to the plausibility that we could be doing a proper randomized trial.

DR. GROSS: Steve?

DR. NISSEN: I just want to come back to something, Tom, and that is that we may be able to refine a bit the equation by doing some of these preliminary studies that I am suggesting. Let me tell you why it helps us. A shorter-term ambulatory blood pressure monitoring study, for example, that might include placebo, amphetamine, methylphenidate and atomoxetine would not expose people to the drugs for very long which, obviously, from the point of view of the safety aspects is very favorable. You would be able to get the kind of heart rate and blood pressure information that would tell you how similar or dissimilar the drugs are. And, it would help a lot if you found out in such a study--I mean, I am going to give you a wild

idea--if you found out that the blood pressure increases were 8 mm or 10 mm with one of these agents--I don't think you would but if you did, that would really inform about whether or not a randomized trial was prudent and acceptable and reasonable to do. That is a short-term exposure so you would get a lot of information.

The second thing we haven't yet talked about is that one of the concerns about these agents is the production of left ventricular hypertrophy. You know, we know that that potential exists and that is a very measurable and very precisely measurable phenomenon with modern echocardiography. So, one of the kinds of studies you could do is, for example, you can take individuals that have had relatively long-term use of the drugs and look at their left ventricular wall thickness in comparison to well-matched controls and you can find out. Again, if you were to see that people that have been on the drug for a year or two had a thicker left ventricle--there is a lot of information about the negative prognostic

implications of left ventricular hypertrophy. So, I would not rule out the value. We don't have any of those mechanistic studies now so we are looking at these data which I know Bob Temple considers to be terribly weak, you know, from the AERS database, and I agree with you, and I am trying to refine our understanding about these drugs by forcing some mechanistic studies that would give us greater clarity and I think they should be done and should be done relatively soon.

DR. FLEMING: By the way, that is in conjunction with, i.e., I completely support what you are saying as insights in conjunction with ultimately the randomized trial where basically those insights give me clues about who are those people that would be more likely to have favorable benefit to risk, and how can I optimally deliver the regimen.

Even with those clues though, my perspective is those clues might help me reduce this risk but if this report says this risk might be 2.5-fold, I am very worried in adults if it is

even 1.5-fold. So, I need those clues to optimally deliver a regimen that, hopefully, is somewhere between no excess risk and 1.5-fold which, in the end though, I am only going to be able to answer reliable with the randomized trial. So, I want what you are doing setting up the randomized trial.

DR. GROSS: Does the FDA have a very clear picture about what we are recommending?

DR. TEMPLE: Yes, but I wanted to praise the last suggestion that Steven made. That is not so different from the studies that were done to document valvulopathy with fenfluramine that David Graham supervised, where you looked at people on the drug and you found a lot of valvulopathy, 5-, 10-fold or something. So, that was sort of a no-brainer once you got the data. But that is actually feasible short term and would overwhelmingly convey the idea that there was a problem in a fairly rapid way. So, that is a pretty attractive suggestion, I have to say. But, yes, I think we probably get the idea.

DR. GROSS: So, it looks as though the

short-term studies recommended would be the simplest, least expensive to do and you would get some good information quite rapidly. Sean and Robyn, did you have comments?

DR. HENNESSY: I have a geek question, and that is, I am interested in proving statistical precision by maybe imposing an assumption. That is, can we do a one-tail test for these safety studies rather than a two-tail test? The assumption then implies that these drugs couldn't provide benefit and what it means is that if we found an apparent beneficial effect we wouldn't believe it. I wanted to know what other people around the table thought about that.

DR. GROSS: Tom?

DR. FLEMING: I guess I think we are routinely doing that. In other words, I don't disagree with it. I agree with it and say we always do that. So, let's say for a superiority setting you are trying to show benefit, we use a two-sided 0.5 standard of strength of evidence. But if you get a two-sided 0.5 you look and see

what direction it is. So, strength of evidence for a single positive study is one-sided 0.25. And, this is all somewhat arbitrary, what is strength of evidence. But at least what has emerged is if something is sufficiently extreme from your hypothesis that it would occur by chance alone one time in 40, we say it doesn't seem attributable to chance. That seems that you have ruled that out. If it is superiority, then you would say, if you had a two-sided 0.5 that is in the right direction, that you have ruled out no effect. This is really non-inferiority. If you are trying to rule out a 1.5-fold increase just using that same strength of evidence it would need to be a result that is inconsistent with 1.5-fold at a 2.5 error rate. So, I would agree with what you are saying but I would say it is what we always do when we are talking about strength of evidence of a two-sided 0.25; it is really one-sided 0.25.

DR. GROSS: John has been waiting for a while. John?

DR. MOORE: I certainly agree with a lot

of the things Tom said, particularly about the children studies. I think that it might be worth considering one additional aspect of it and that could be, biting the bullet if you will, studying the problem in children who have cardiovascular risk factors. One of the testimonies earlier referred to that, a case in Children's Hospital. But I think we do know that probably 40 or 50 percent of children who have post-op congenital heart disease, which is a fairly large number of children these days, have ADHD.

Another interesting piece of data is that only probably 8 percent of them or 10 percent of them are actually treated. The reason is that I think most practitioners are afraid to treat them. I think that a structure exists already that is NHLBI funded, called the Pediatric Heart Network, which is probably capable of doing a randomized study of this subset of the pediatric population, which could be adequately powered to look at safety at least at some level and maybe help us bracket safety, at least in this high risk population.

I think that that study could be done and could be done ethically by that group. In fact, I think such a study has been proposed and may be under discussion by them. So, one of the things the FDA might want to do is link up with NIH and inquire about the Pediatric Heart Network and that study in particular. The lead investigator would be Vickie Better [?] out of CHOP, Children's Hospital Philadelphia. But I think that it might be useful to add that to a more observational approach for the general population to help us get at the risk in children.

Again, you know, I feel that these drugs are so beneficial to a lot of children that it is important not to inhibit their use too much. But, on the other hand, we do have sort of this group of patients that are unidentified who have cardiovascular problems and those are the patients I think where the serious issues arise. But why don't we just try to study them directly? We can identify a large group of patients with hypertrophic cardiomyopathy and this problem. We

can identify a large group of patients who have congenital heart disease and ADHD. Why not study them directly?

DR. GROSS: Robyn?

MS. SHAPIRO: Just a couple of comments about the ethics. First, I don't think that we can simply clear our minds by saying, well, people are fully informed about the risk and if they take it then, you know, we are okay. As we know, a reasonable risk/benefit balance is something that IRBs have to consider, and so forth--fully incorporated into our federal law.

But if we talk about Tom's large, adequately powered trial for adults, the alternatives I think are less ethical than going forward with that. We could do nothing, in which case we know that these are being prescribed more and more and we have these safety signals but we will never know what is going on. Or, we could do a less scientifically, biostatistically adequate trial, in which case we will expose those people to the risk but not really get an answer. So,

ethically I think that the only way to do that trial, from what I hear Tom say, is to do it his way.

DR. GROSS: Steve?

DR. NISSEN: I think we may have a problem, maybe even a show-stopper here, Tom, and that is that as I look at the labels, which of these drugs are labeled for use in adults for adult ADHD? It is not all of them. I can't find it for the others. Maybe it is something I am not aware of but if, in fact--you know, then we have an additional issue here I think, don't we?

DR. FLEMING: I am not sure what issue. Basically, you are saying because of the fact that we can only study those labeled--

DR. NISSEN: No, you made a very eloquent argument that equipoise exists because the drug have proven benefits and, therefore, since there is risk in the face of proven benefits there is equipoise. But in the face of unproven benefits the equipoise equation starts to fall apart, doesn't it?

DR. FLEMING: So, if you are arguing that there is such uncertainty about benefit here that we couldn't get people, when they were properly informed about what is known about benefit to risk, to have a sense of equipoise, then not doing this trial leaves me enormously concerned because we have a million and a half adults already using this agent. Obviously, they must think that it is in their benefit. I would think someone, to use an agent, would have made a judgment--I am not sure how informed they are but they will have made the judgment that this is, in fact, something they should do. Are you saying that if we, in fact, gave them proper informed consent most of those people would say now they aren't even at a position of equipoise? They don't want to use the agent?

DR. NISSEN: I guess I am only raising that it does shift the equation because, you know, some folks here have argued that a ten year-old that is bouncing off the wall in school--and, by the way, I know there are kids out there that are getting enormous benefit from these drugs and I buy

that, although I am not sure it is ten percent of all ten year-olds that are getting that benefit. But having said that, you know, what if, Tom, the drugs actually don't work in adults? What if they really don't work?

DR. TEMPLE: [Not at microphone; inaudible].

DR. NISSEN: All right, so it is just Ritalin. That helps a little bit. So, they actually have adequate evidence. That helps.

DR. GROSS: Ralph?

DR. D'AGOSTINO: I have two comments, one in terms of the ethics. A retrospective look at existing databases is, in fact, ethical so I think you could answer a lot of questions with that.

The other comment I want to make is about the one-sided versus two-sided. I think that there is a potentially really serious issue, and it is not so much one-sided, two-sided, it is that the sample sizes and the event rates aren't going to be large enough to rule out risk like 1.5. They are going to rule out things like 3 and I think you are

going to have a real question in terms of how big is the study and what kind of risk you have adequate power to rule out, and is that going to be sort of acceptable for the FDA and for the scientific community to feel comfortable with? And, I think some of the things you can hope for is ruling out a very large risk and that is going to be uncomfortable.

DR. FLEMING: Just on that point, that is a key point. And this was my position, we should be ruling out something less than 3; we should be ruling out 1.5. That takes 250 events. So, the question is, is it plausible to randomize and follow enough people such that 250 events will have a cardiovascular death, stroke or MI?

DR. D'AGOSTINO: I think you can do it in the adults--

DR. FLEMING: That is what I am saying. So, given the high rate in adults of 100 per 10,000 even in the control arm, this is identical--this is now identical to the scenario we are confronting today with the COX-2s where we are proceeding with

additional studies of this size, of the size of about 7,000 or 8,000 per arm to more responsibly understand with the COX-2s is the risk 1 or 1.5 for classes of agents that would be used by patients today. So, we are just saying we would do the same thing in this context.

DR. GROSS: Let's move on to the next question, number four, what are the important confounders relating to use of ADHD drugs in both children and adults that should be considered in a study of ADHD drugs and cardiovascular outcomes?

DR. D'AGOSTINO: You know, in the adults the usual cardiovascular risks--the age, gender, blood pressure, cholesterol, smoking, diabetes, preexisting clinical disease, would have to be carefully brought into it, and make sure that we have adjustments in the analyses.

For the children it sounds like it is more structural abnormalities and we obviously look at other cardiovascular type of risk. But it seems that it is more the structural abnormalities that really might be confounders.

DR. GROSS: So, those would have to be looked for initially.

DR. D'AGOSTINO: Exactly. These large hearts, do they start off normal size and they get larger and larger with the drug? That has to be monitored also but certainly at the initial baseline.

DR. GROSS: Anyone else? Yes, Marsha?

DR. RAPPLEY: I think it was mentioned earlier but it is important to look at regional patterns of use because they vary greatly both in diagnosis and in use of medications. Then what might be harder to get at is the genetic predisposition that people may have towards heart disease, particularly when we are looking at children advancing into young adults rather than adulthood and what is cumulative risk there. I have been impressed with the data retrieval that can come out of the Kaiser system and the other similar electronic records that might give some insight into that. But, again, I guess what I am suggesting is that there might be multiple and

simultaneous designs and methods that are complementary to one another as we try to triangulate this issue.

DR. GROSS: And about the drugs that might be confounders?

DR. RAPPLEY: There is a whole slew of drugs that would affect behavior, and we know that children with chronic illness, very widely defined, have a much higher incidence of attention deficit hyperactivity disorder and that children with ADHD also have a higher incidence of chronic disease, but it is not as high as the other way around. Then particular medications, many of them which are very commonly used, the asthma medications, the antisteroidal anti-inflammatories are associated with changes in behavior and activity level and cognition. So, there are many, many drugs that would have to be accounted for, a list of medications.

DR. GROSS: Annette?

DR. STEMHAGEN: I think there are a couple of things. In part of the FDA analysis of the

spontaneous reports there was a lot of concomitant medication--actually not concomitant medication but illicit drug use, drug abuse, those kinds of things. It is very difficult to get at in a prospective study; impossible to get at in a database study but it seems like there was a lot of that in a lot of the spontaneous reports. So, trying to think about whether there is a way to do that, whether there are some of these databases where you can actually also do patient interviews, if that is possible, might be something to think about. So, I would look at the spontaneous reports and look at some of those other possible confounders and see if there is a way we could collect that data.

DR. GROSS: Sean and then Arthur.

DR. STEMHAGEN: Just one other thing, I think the broad range, if we are looking at pediatrics 0-19, there probably are very different confounders between 0-10 and 10-19 so we need to carefully think about that as well.

DR. HENNESSY: ADHD clearly isn't

schizophrenia but in using schizophrenia as a model in studying cardiac effects of any psychotic medications we know that patients with schizophrenia have higher rates of cardiovascular outcomes apart from treatment, and one of the hypotheses for that is endogenous catecholamine. If the same is true of ADHD, then the drugs may look like they are associated with the outcome by means of confounding indication and it may be worth doing some catecholamine studies on untreated children with ADHD to see whether that is the case.

DR. GROSS: Anyone else? Yes, Marsha?

DR. RAPPLEY: I think compliance is a major issue too and it is something that is very difficult to get at but, again, if you could do chart abstraction of electronic records it might give some insight into that. You cannot do that, of course, in the claims data.

DR. GROSS: Sean?

DR. HENNESSY: There actually have been some studies looking at refill adherence as a predictor of taking pills as measured by medication

monitors on the pills. Actually, refill adherence is a fairly good measure of that. So, while you don't necessarily know when they are taking it, if they show up every 30 days for a new prescription that is a pretty good sign that they are taking the drug close to as directed.

DR. GROSS: I think everybody but Sean is running out of energy so let's move on to number five, please discuss study approaches that may explore duration of use of ADHD drugs. Specifically, consider whether there are feasible study methods that could be undertaken to characterize longer-term cardiovascular risk, in any age group, with chronic ADHD drug therapy. Steve?

DR. NISSEN: I want to bring up again the possibility--I recognize that the mean or median use is 8 months but there must, in fact, be a number of people out there who have been exposed for longer periods of time. So, the ability to look for structural abnormalities that might be expected with long-term use of a drug that

increases blood pressure and heart rate--you know, because of the animal model of chronic amphetamine use as a way to induce cardiomyopathy exists, then one could look at ventricular function, so ejection fraction--pretty simple. If somebody has had two years, three years or four years of exposure, you know, to measure ejection fraction and compare it to matched controls. If you see that there is on average a lower ejection fraction--I know, Bob, you are concerned about heart failure and I am concerned as well as a late long-term consequence. One of the ways to look at it is to use these very elegant methods that we have to see whether long-term use is associated with structural changes--chamber size, contractility which can be measured precisely in studies that are not enormous in size.

DR. GROSS: Oh, come on, the group can't be that silent!

DR. DAVIS: I have a question for Tom.

DR. GROSS: Yes?

DR. DAVIS: These randomized, controlled

trials, how long are you thinking they are going to last?

DR. FLEMING: It obviously depends on the success we have in defining a control regimen that is a standard of care that someone would appropriately be kept on for a long time.

DR. DAVIS: But how about the intervention group? They bail out after six months.

DR. FLEMING: What is the goal here? When we look at this question, there are two aspects to this question. I guess you will be sad you threw down the gauntlet and said we were too tired to keep talking--[Laughter]--there are two aspects to this that are important. One is when you are delivering a regimen that involves one of these agents if there are risks, are those risks only apparent early on? Do they emerge over time even after you have stopped therapy? That is one set of questions. Another set of questions would be if you give intended different durations, does that have an impact on risk? So, can you use something for only a short period of time and not have risk

but if you use it for too long a period of time you have increased risk? That second question technically can only be answered rigorously by randomizing to those strategies, a strategy of non-use, a strategy of using for six months and a strategy of using for an indefinite period of time, following the entire time-zero cohort in time. That is one of the elegant aspects of a randomized trial. It allows you to reliably answer that question.

The temptation is to use an observational database and see what is the risk level for somebody who is on it for three months, somebody is on it for six, somebody is on it for nine. Well, the problem with that is you are presuming that there are no inherent differences in people who are on it for shorter versus longer times. And, if you see an association with risk for those that are on long versus short, is it due causally to the fact that you gave it a long time or because those people who took it for a long period of time were intrinsically different? I don't know the answer

to that. If I have no ability to do a randomized trial I will use those data to generate a hypothesis but ideally I would like to address that with a randomized trial.

The first issue though is when you deliver an agent from this class versus not delivering an agent from this class--and people will be on it for however long it is appropriate in their judgment and their caregiver's judgment to be on it so it is a real-world setting. In that real-world setting, how does risk emerge? Is there any excess risk at all and, if it does emerge does it emerge early or does it emerge late? I mentioned the Vioxx trials, the VIGOR and APPROVE trials, that suggest that it is not just being on Vioxx, it is when you have been on Vioxx the differences begin to emerge more significantly after 18 months. Now, that doesn't tell me that if I stopped at 12 I would get rid of the risk but at least it gives me a sense of the time frame over which the risk occurs and a randomized trial would be the ideal way to get at that. Ideally, that would mean that if it is

adequate to only know over a year, then a year is fine. But if the profile is different in the second year from the first I should, in fact, do a two-year trial. If we can come up with a standard of care that doesn't involve these agents for two years, then a two-year trial is feasible. If not, you may be limited to a one year. But my preference would be, not knowing what that risk profile is over time, I would like to see a controlled trial that would ideally follow over two years. It doesn't mean you have to stay on the original randomized regimen; it is the original randomized regimen followed by best standard of care versus control followed by best standard of care and my only constraint is I don't want the controls crossing into the very agent that I am trying to assess safety for. That is my only restriction.

DR. GROSS: Sean, you are still going?

DR. HENNESSY: Spontaneous reports might be helpful in figuring out how long we need to go out but looking at the duration of treatment in the

people who developed disease and who were reported.

DR. GROSS: Thank you, all. I was going to say the meeting is almost over. I know Marsha has a comment but Tom and Sean can carry on afterwards. Marsha, go ahead.

DR. RAPPLEY: I just think we need to expand our sense of long term around this diagnosis issue because we now have a segment of people who are treated throughout their school years into their young adult years and beyond. So, we will need these observational studies I think to tap into that duration over that period of time.

DR. GROSS: To the FDA, you have asked some very difficult questions. I hope we have been some help. Our committee will reconvene tomorrow at eight o'clock. All of the committee members are invited to dinner this evening. Mary Grosse will be the organizer and we will meet in the lobby at 6:15. Thank you, all.

[Whereupon, at 4:40 p.m., the proceedings were recessed, to reconvene Friday, February 10, 2006 at 8:00 a.m.]