Food and Drug Administration
Office of the Commissioner

Summary Minutes of the
PEDIATRIC ETHICS SUBCOMMITTEE
of the
PEDIATRIC ADVISORY COMMITTEE

September 10th, 2004

Members Present
Robert M. Nelson, M.D., Ph.D. (chair)
P. Joan Chesney, M.D.
Richard Gorman, M.D. (Pediatric Health Organization Representative)

FDA Participants
Dianne Murphy, M.D.
Sara Goldkind, M.D., M.A.

Office for Human Research Protections Participants
Bernard A. Schwetz, D.V.M, Ph.D.
Julia Gorey, J.D.

Executive Secretary
Jan. N. Johannessen, Ph.D.

Consultants to the Pediatric Advisory Committee
Norman Fost, M.D., M.P.H.
Laurence L. Greenhill, M.D.
Ruth Hughes, Ph.D., CPRP (Patient-Family Representative)
Janis E. Jacobs, Ph.D.
Eric Kodish, M.D.
Mary Faith Marshall, Ph.D.
Diane Treat (Patient-Family Representative)
Tonya Jo Hanson White, M.D.

Open Public Hearing Speakers:

?? Vera Sharav – Alliance for Human Research Protection

?? Alan Milstein

FDA and OHRP Presentations:

Subpart D Expert Panel Process	Bernard Schwetz, D.V.M, Ph.D. Director, Office for Human Research Protections
	Sara Goldkind, M.D,. M.A. Bioethicist, Office of Pediatric Therapeutics, FDA

Subcommittee Presentations:

Overview, Charge to Panel and Final Outcome	Robert M. Nelson, M.D., Ph.D. Chair, Pediatric Ethics Subcommittee
Summary of Submitted Public Comments	Robert M. Nelson, M.D., Ph.D. Chair, Pediatric Ethics Subcommittee

Guest Presentation:

Background on ADHD/Protocol Overview	Judith L. Rapoport, M.D. Principal Investigator, NIMH

Questions to the Committee:

(1) What are the potential benefits of the research, if any, to the subjects and to children in general?

There is no direct health benefit to the children included in the research. The protocol addresses the question of a unique central response to stimulants in ADHD, utilizing a better research design than previously published studies and controlling for performance differences. As such, the protocol may be able to untangle clinical state and trait (i.e., degree of genetic relatedness) differences through the use of monozygotic and dizygotic twins who are discordant for ADHD. More speculatively, the results may improve our understanding of ADHD in order to enhance diagnostic precision and avoid misclassification and overtreatment.

(2) What are the types and degrees of risk that this research presents to the subjects?

The Subcommittee found that the interventions and procedures contained in the research fell into two different degrees of risk. Apart from withholding medication for 36 hours for the ADHD subjects and the blinded administration of study drug to subjects both with and without ADHD, all of the other procedures present no more than minimal risk utilizing the risk reduction strategies as outlined in the protocol. Withholding medication for 36 hours for the ADHD subjects and the blinded administration of study drug to subjects both with and without ADHD present more than minimal risk, but is limited to a minor increase over minimal risk.

(3) Are the risks to the subjects reasonable in relation to the anticipated benefits, and is the research likely to result in generalizable knowledge about the subjects' disorder or condition?

For all subjects enrolled in the research, the risks to subjects are reasonable in relation to the importance of the knowledge (i.e., benefit to children in general) that may reasonably be expected to result. However, it is only for the children with ADHD that the research is likely to yield generalizable knowledge which is of vital importance for the understanding of the subjects' disorder. The children without ADHD do not have a disorder or condition, although the brain

response of children without ADHD to a single dose of Dextroamphetamine is an important part of the generalizable knowledge to be gained by this research.

(4) Does the research present a reasonable opportunity to further the understanding, prevention, or alleviation of a serious problem affecting the health or welfare of children?

Yes

For details of all presentations and discussions, please see the full transcript of this meeting.

In addition to providing answers to the questions, the Subcommittee had a number of recommendations, which are included in the Chair's summary of the meeting. This meeting summary was also presented to the Pediatric Advisory Committee on September 15, 2004 and can be found at the dockets website for that meeting. It is also included below.

Chair's summary of the
Pediatric Ethics Subcommittee meeting
September 10, 2004

I. Introduction

A. The Pediatric Ethics Subcommittee of the Pediatric Advisory Committee (hereafter, the Subcommittee) met on September 10, 2004, to review the research protocol "Effects of a Single Dose of Dextroamphetamine in Attention Deficit Hyperactivity Disorder: A Functional Magnetic Resonance Study" referred by the IRB of the National Institutes of Mental Health under 45 CFR §46.407 and 21 CFR §50.54. This report contains the recommendations and determinations of the Subcommittee that will be presented to the Pediatric Advisory Committee on September 15, 2004. After speaking to the determination of the risks associated with the interventions and procedures in the research, the Subcommittee offers specific design recommendations, and required modifications to the research protocol and to the process and documentation of parental permission and child assent. Assuming those modifications are made, the Subcommittee responded to specific questions concerning the research, and recommends that the research is approvable (assuming these modifications) under 45 CFR §46.406/21 CFR §50.53 and 45 CFR §46.407/21 CFR §50.54. Finally, although not discussed by the Subcommittee, this report addresses an issue raised in public comments, specifically the applicability of Ericka Grimes v. Kennedy Krieger Institute, Inc., 82 A. 2d 807 (August 16, 2001) to the research.

II. Subcommittee Determination of Risk

A. The first criteria for IRB approval of research is that the risks to subjects are minimized by using procedures which are consistent with sound research design and which do not unnecessarily expose subjects to risk (45 CFR §46.111). The Subcommittee made specific recommendations and stipulations (detailed below) for modifications to the protocol, parental permission and child assent process and documents which would assure that the risks are minimized. Provided that these modifications are made, the Subcommittee made the following determinations concerning the risks associated with the interventions and procedures contained in *the research.*

B. The Subcommittee determined that the risk associated with taking a single 10 milligram dose of Dextroamphetamine for a child between the ages of 9 and 18 years (both subjects with and without ADHD) is more than minimal risk, but is limited to a minor increase over minimal risk.
   1. A single dose of Dextroamphetamine is more than minimal risk because the adverse effects that might occur (noted below) are more than those expected in a routine visit to a doctor.
   2. A single dose of Dextroamphetamine is no more than a minor increase over minimal risk because…
      a) Dextroamphetamine has been used for children with ADHD since 1937 and unexpected but serious adverse events have not been reported.
      b) The only stimulant medications approved down to age 3 are Dextroamphetamine and mixed salts of amphetamine (Adderall).
      c) The greatest side effects reported from an idiosyncratic reaction to Dextroamphetamine are increased irritability, restlessness, agitation, and temper outbursts that last no more than 4 to 5 hours, with no sequelae later in the day.
      d) Dextroamphetamine is universally used in pediatric practice within the United States.
      e) The more common risks of Dextroamphetamine are mild restlessness, anxiety, loss of appetite, and insomnia.

C. The Subcommittee determined that the risk associated with the other interventions and procedures (apart from withholding medication for 36 hours from the ADHD subjects and the blinded administration of study drug to subjects both with and without ADHD) contained in the protocol (assuming that the above modifications are implemented) present no more than minimal risk for a child between the ages of 9 and 18 years (both subjects with and without ADHD).

D. The Subcommittee determined that the risk associated with withholding medication for 36 hours for the ADHD subjects is more than minimal risk, but is limited to a minor increase over minimal risk. Often, children with ADHD do not receive stimulant medication over a weekend. In addition, the risks of withholding medication for ADHD are inattentive and hyperactive behaviors.

III. Design Recommendation

A. The Subcommittee had concerns about whether the scientific benefits might be limited by the proposed design. As reflected in the Common Rule (i.e., Subpart A), a central ethical principle is that the risks of the research should be reasonable in relation to anticipated benefits, if any, to subjects, and the importance of the knowledge that may reasonably be expected to result. Accordingly, the following recommendations are proposed:

B. Subject Inclusion
   1. Given the variability in neurodevelopmental stages and response to stimulants in the proposed subject population (i.e., 9 – 18 years of age), the Subcommittee strongly encourages the investigators to narrow the age range to either the younger (i.e., 9 – 12 years of age) or older (i.e., 13 – 18 years of age) children.
   2. To reduce the confounding variable of prior drug exposure for the children with ADHD, the Subcommittee strongly encourages the investigators to restrict the ADHD subjects to either those who as yet have not been exposed to treatment with stimulants (i.e., treatment naïve) or those who fall within a more uniform (and lower) range of stimulant dose (e.g., 10 to 25 milligrams). In addition, stratification of data about prior treatment (e.g., duration of exposure, dose) should be considered in the data analysis.

IV. Required Modifications of the Protocol

A. The interventions and procedures performed in the protocol are not clearly stated in one place. For example, the schedule of procedures to be performed at each visit (see page 11) is incomplete. The description of the interventions and procedures should be complete and easily accessible in one section. The Subcommittee, in reviewing the protocol, identified the following procedures for the purpose of making a determination. Phase One (screening) includes: (1) telephone and mail screening (recruitment); (2) physical and neurological examination (all subjects); (3) neuropsychological assessment (i.e., a full-scale WISC-III testing and K-SADS interview for all subjects, and a structured Psychiatric Interview, including Child Behavior Checklist for non-ADHD controls); (4) DNA cheek swab for determining genetic relatedness (twins only); (5) a practice functional MRI session using the "stop" task; (6) a determination of ADHD phenotype (ADHD subjects, including ADHD twins) using Structured Interview and Rating Scales (both parent and patient), Connors Teacher Rating Scale, and Teacher Report Form; (7) a similar assessment of the non-ADHD controls (including non-ADHD twins), using a telephone interview, Parent and Teacher Rating Scales, an in-person assessment, and, if necessary, Family Interview of Genetic Studies; and (8) pregnancy testing. Phase Two (testing) includes: (1) withholding medication for 36 hours for the ADHD subjects; (2) two functional MRI sessions (drug/placebo) while performing two (or three) tasks; (3) single 10 milligram oral dose of Dextroamphetamine (compared to single oral dose of placebo); (4) Motivation Survey (after each MRI session); and (5) Performance Tasks, including (a) Stimulus-controlled go/no-go task, (b) "Stop" task (controlled for performance), and an optional alternate Go-No-Go task (if time permits, with total MRI session not to exceed 90 minutes). The Subcommittee also learned during the investigator presentation that a diagnostic MRI scan will be performed on all subjects. This information is not contained in the protocol or parental permission and child assent documents.

B. The sequence of subject testing to minimize the risk exposure of children to the interventions and procedures in this protocol is not clearly spelled out in the protocol. The investigator stated (and the Subcommittee agrees) that the unrelated subjects with ADHD and the non-ADHD controls will be studied first. Only if differences in the functional MRI are found between these two groups will the two twin cohorts be studied. Although there are hints of this sequence in the protocol (e.g., the last paragraph of the Precis; page 5 "If ADHD subjects differ from controls…"; and page 19 "10 healthy subjects will be piloted…"), this approach needs to be explicitly stated.

C. Dosing of Dextroamphetamine/Placebo

1. The protocol contains a number of discrepancies in the dose of the administered drug. These need to be clarified.
    a) The Subcommittee understood the dose of the Dextroamphetamine to be a single dose of 10 milligrams, and the lower weight limit for eligible children to be 40 kilograms (to assure that no one exceeds a dose of 0.25 mg/kg). The protocol and parental permission documents should be modified accordingly.
2. In order to minimize the risks of the drug administration, it should be given in the morning.
    a) The fMRI study should be conducted in the morning so that the single dose of the drug is administered in the morning. This will assure that any effect of the drug has dissipated by the afternoon or early evening. If the drug is administered late in the day, the child potentially would be unable to fall asleep that night.

D. Functional MRI

1. The protocol lacks sufficient discussion of the precautions taken to minimize psychological risk with the fMRI testing. Specifically, more information should be provided about the training session, such as screening measures taken to exclude children who are claustrophobic or fearful of being in the MRI scanner. The use of the head cushion should be described, including the fact that uncomfortable restraints will not be used. According to the protocol

(page 15), the operation of the 3 Tesla scanner will remain within the FDA standards for a "minimal risk" MRI.

E. Diagnostic MRI
   1. There is no mention in the protocol or the parental permission/child assent documents of a diagnostic (as opposed to functional) MRI scan. This information needs to be provided. In addition, the parent should be informed about the possibility of an abnormality being found, including the chance of a false positive or a finding of uncertain importance. Information should be provided about the follow-up of any positive findings, including any financial implications.

F. Pregnancy Exclusion
   1. Information about pregnancy testing needs to be added to the protocol, and the parental permission and child assent documents. There is no mention of whether the pregnancy testing is being done with blood or urine. The protocol should include a discussion of the process by which this information will be discussed with the adolescent and/or parent, what information will be disclosed to the parent, the protection of adolescent confidentiality in soliciting information about sexual activity, and so forth. The parent permission document needs to include a discussion of whether (and how) this information will be shared with the parent and child.

G. Neuropsychological Testing
   1. The results of the neuropsychological testing should not be made available to parents, as these are not being performed for diagnostic or treatment purposes. The parent needs to be aware that the child may be excluded from taking the WISC-III for one year, given concerns about scores being affected by repeat performance. As the protocol is not intended to offer direct benefit, the inclusion of clinical care and consultation is inappropriate and may create a parental misperception of therapeutic benefit.

H. Genetic Testing
   1. Genetic testing should be restricted to determining zygosity (i.e., genetic relatedness). The protocol contains no discussion of any risks related to the selected markers, nor any storage for the purposes of future testing. As such, samples should be destroyed after the DNA analysis of the listed markers. In addition, the data on the individual markers should be destroyed once zygosity has been determined for any given twin pair.

V. Modifications to Parental Permission and Child Assent Process (and Documents)

A. The parental permission and child assent documents need to include a more complete discussion of the procedures included in the protocol. The discussion should be in chronological order, grouped according to visit. Specifically, information (including risks) should be included about: screening tests (including teacher contact), diagnostic MRI, pregnancy testing, the series of functional MRI sessions, including the training session, timing and dosing of the drug (and that it is a liquid and not a pill), and that there will be no provision of test results to parents, including information about exclusion from re-taking the WISC-III for one year.

B. Payment for Participation
   1. The payment for participation in the research is excessive. In addition, it is not clear who will receive the payment. The parent should receive compensation for expenses. The child should receive a nominal payment for participation, with an acceptable range between a token of appreciation (for younger children) and an age-appropriate hourly "wage" (for adolescents). Based on the estimated time of 11 hours to complete the entire study, the Subcommittee discussed a total compensation of about $100-110 as more appropriate for the child, in addition to reimbursement for any direct expenses (transportation., meals, etc). The compensation should be divided fairly across each phase of the protocol so that a child who desires to withdraw will still be compensated for the time involved to that point.

C. Process of Assent and Opportunity to Dissent
   1. The process by which a child will be asked to assent to participate in the research needs to be described. Special attention needs to be paid to providing a child the opportunity to dissent, especially for the twin pairs.

D. Any language about "treatment" should be deleted from the assent and permission documents, and clear language about the lack of any direct benefit should be added.

E. The parental permission document should include the reassurance that the genetic testing being performed in this study on the twins cohorts is not likely to lead to insurance discrimination. Destruction of the samples after they have served the purpose of determining zygosity will ensure that there is no risk of additional genetic testing.

F. Risks of the Study Drug
   1. The parental permission document should clarify that there is no risk of addiction from one dose of Dextroamphetamine administered in the context of a research protocol, although it is classified as a "drug of abuse." Possible confusion with "methamphetamine" should be clarified, perhaps using the distinction between "substance abuse" and "addiction."
   2. The risks of the Dextroamphetamine dose need to be clearly and completely described, using the categories of "frequent", "infrequent" and "rare".
   3. The language about "falling within the range of [normal] experience" should be deleted.

G. The permission of both parents is required for a child to participate in the research, unless one parent is deceased, unknown, incompetent, or not reasonably available, or when only one parent has legal responsibility for the care and custody of the child.

H. Throughout the parent permission document, there is technical language which is not explained in lay terminology. In addition, the parent permission and child assent form should detail an alternative to participation even if it is merely not to participate in the case of controls and to receive standard care in the case of ADHD patients.

VI. Summary Response to Specific Questions

A. What are the potential benefits of the research, if any, to the subjects and to children in general?
   1. There is no direct health benefit to the children included in the research. The protocol addresses the question of a unique central response to stimulants in ADHD, utilizing a better research design than previously published studies and controlling for performance differences. As such, the protocol may be able to untangle clinical state and trait (i.e., degree of genetic relatedness) differences through the use of monozygotic and dizygotic twins who are discordant for ADHD. More speculatively, the results may improve our understanding of ADHD in order to enhance diagnostic precision and avoid misclassification and overtreatment.

B. What are the types and degrees of risk that this research presents to the subjects?
   1. As discussed above, the Subcommittee found that the interventions and procedures contained in the research fell into two different degrees of risk. Apart from withholding medication for 36 hours for the ADHD subjects and the blinded administration of study drug to subjects both with and without ADHD, all of the other procedures present no more than minimal risk utilizing the risk reduction strategies as outlined in the protocol. Withholding medication for 36 hours for the ADHD subjects and the blinded administration of study drug to subjects both with and without ADHD present more than minimal risk, but is limited to a minor increase over minimal risk.

C. Are the risks to the subjects reasonable in relation to the anticipated benefits, and is the research likely to result in generalizable knowledge about the subjects' disorder or condition?
   1. For all subjects enrolled in the research, the risks to subjects are reasonable in relation to the importance of the knowledge (i.e., benefit to children in general) that may reasonably be expected to result. However, it is only for the children with ADHD that the research is likely

to yield generalizable knowledge which is of vital importance for the understanding of the subjects' disorder. The children without ADHD do not have a disorder or condition, although the brain response of children without ADHD to a single dose of Dextroamphetamine is an important part of the generalizable knowledge to be gained by this research.

D. Does the research present a reasonable opportunity to further the understanding, prevention, or alleviation of a serious problem affecting the health or welfare of children?
   1. Yes.

VII. Subcommittee Determination of Approval Categories

A. Consistent with the referring IRB analysis, the procedures and interventions included in the research can be approved for the children with ADHD under 45 CFR §46.406 and 21 CFR §50.53. The research or clinical investigation does not hold out the prospect of direct benefit for the individual subjects. Nevertheless, (a) the risk represents a minor increase over minimal risk; (b) the intervention or procedure presents experiences to the children with ADHD that are reasonably commensurate with those inherent in their actual or expected medical, psychological, social, or educational situations; (c) the intervention or procedure is likely to yield generalizable knowledge about the subjects' disorder or condition which is of vital importance for the understanding or amelioration of the subjects' disorder or condition; and (d) adequate provisions are made for soliciting assent of the children and permission of their parents or guardians, as set forth in §46.408 and §50.55.

B. The referring IRB found that the proposed research presents a reasonable opportunity to further the understanding of a serious problem affecting the health or welfare of children, but that the involvement of children without ADHD could not be approved under §46.404/§50.51, §46.405/§50.52, or §46.406/§50.53. The Subcommittee determined that, if appropriate changes are made, (a) the research presents a reasonable opportunity to further the understanding of a serious problem affecting the health or welfare of children; (b) the research will be conducted in accordance with sound ethical principles; and (c) adequate provisions are made for soliciting the assent of children and the permission of their parents or guardians, as set forth in §46.408 and §50.55. As such, the Subcommittee recommends that the involvement in the research of children without ADHD is approvable (assuming all of the required modifications are made) under 45 CFR §46.407 and 21 CFR §50.54.

VIII. Other Issues

A. Applicability of Ericka Grimes v. Kennedy Krieger Institute, Inc., 82 A. 2d 807 (August 16, 2001)
   1. General Comment
      a) The question of the applicability of the holding of Ericka Grimes v. Kennedy Krieger Institute, Inc. to the protocol under deliberation was addressed by FDA and OHRP attorneys to the Chair prior to the Subcommittee meeting, and was not discussed at the Subcommittee meeting.
   2. As the protocol under consideration is a single site study within Maryland, the question of the applicability of the holding in Ericka Grimes v. Kennedy Krieger Institute, Inc. (2001) can be addressed. Briefly, the holding is not applicable to the current referral for the following two reasons.
      a) The National Institutes of Health (NIH) enclave is subject to exclusive Federal jurisdiction, and therefore is not subject to State law unless the Federal government has acquiesced to State law application. Given this, the Maryland Court of Appeals' holding in Ericka Grimes v. Kennedy Krieger Institute, Inc., 782 A. 2d 807 (August 16, 2001),

does not affect research involving children that is conducted by NIH researchers at NIH or on NIH property.

b) Moreover, even if a proposed clinical investigation would take place on property in Maryland not subject to Federal jurisdiction, it is not clear in what way the Grimes case would affect such a trial. In denying the motion for reconsideration, the Maryland Court of Appeals stated that "the only conclusion that we reached as a matter of law was that, on the record currently before us, summary judgment was improperly granted." Therefore, the rest of the Court's opinion, including any statements it made regarding whether in Maryland a parent can consent to the participation of a child in nontherapeutic research where there is any risk of injury, technically is dicta and as such is not directly binding. Moreover, this unusual and controversial statement was later modified by the presiding judge.

I certify that I attended the September 10, 2004 meeting of the Pediatric Ethics Subcommittee of the Pediatric Advisory Committee and that these minutes accurately reflect what transpired.

Jan N. Johannessen, Ph.D.
Executive Secretary

Robert M. Nelson, M.D., Ph.D.
Chair