DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

National Institutes of Health
National Institute of Mental Health

Date: 3/5/04

From: Chair, NIMH IRB

Subject: Request to Forward NIMH Protocol to DHHS for Review

To: Michael Gottesman, Deputy Director

On behalf of the NIMH IRB I am respectfully requesting that the attached protocol: Effects of a Single Dose of Dextroamphetamine in Attention Deficit Hyperactivity Disorder: A Functional Magnetic Resonance Study be forwarded to the Department of Health and Human Services for review by a "407 panel" as required under 45CFR46.407.

Briefly, this protocol involves the administration of a single, 10 mg dose of dextroamphetamine in conjunction with functional magnetic resonance imaging (fMRI) in healthy volunteer children and children with Attention Deficit Hyperactivity Disorder (ADHD). The central question raised by this protocol is whether the administration of dextroamphetamine to healthy children is permissible under the federal regulations as a minimal risk procedure.

The protocol has been reviewed extensively. It underwent scientific review by both internal NIMH scientists and extramural scientists and received very strong endorsements for its scientific importance, design, and methodology. The NIMH IRB then performed a very comprehensive review. Although the official vote of the NIMH IRB was divided (please refer to the attached IRB minutes), the final decision of the Board was that this is a study which offers no direct medical benefit to participants but has scientific merit. However, the IRB determined that it was not approvable under 45 CFR 46 because the administration of dextroamphetamine posed more than minimal risks to healthy children. The protocol was also the topic of Clinical Center Ethics Grand Rounds on March 3rd, 2004. Consistent with the NIMH IRB recommendation, the invited discussant for this Grand Rounds presentation recommended forwarding this study to a "407 panel."

At each level of review and discussion, this protocol generated animated debate with respect to the appropriate interpretation of "minimal risk" and under what circumstances healthy children could be given medications for research purposes. Attached to this memorandum are copies of the protocol, consent forms, the science reviews, and the IRB minutes relevant to this protocol. Key issues identified by the Board are as follows:

- Possible risks to a healthy child from exposure to a psychoactive controlled substance (albeit a single dose). Several IRB members expressed the concern that a child participant in this study might subsequently conclude that experimentation with stimulants or related substances of abuse (e.g., cocaine) was not a hazardous activity.

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- In contrast, several Board members considered a single dose of dextroamphetamine to pose only minimal risks since the likely acute physiological and psychological effects of this medication were commensurate with risks ordinarily encountered in the daily lives of children (e.g., equivalent to participation in contact sports, heavy caffeine consumption, etc.).
- The proposed compensation for the study (up to $570) may constitute an undue inducement for potential study subjects and/or their parents.

If you have any questions related to this protocol or the IRB review process, please to not hesitate to contact me. Thank you for your consideration of this request.

Donald L. Rosenstein, M.D.