2. Correspondence dated March 4, 2005 from UC Institutional Review Board A, Division of Biological Sciences to the UC Associate Vice-President for Research requesting HHS review, pursuant to 45 CFR 46.407, the above reference protocol.

The Division of Biological Sciences • The Pritzker School of Medicine
The University of Chicago Hospitals

Institutional Review Board
5841 S. Maryland Ave.
AMB S-138 • MC 1108
Chicago, Illinois 60637
(773) 702-6505

Mary Ellen Sheridan, Ph.D. March 4, 2005
Associate Vice-President for Research and
Director of Research Administration
The University of Chicago
970 E. 58th St., 3rd fl
Chicago, Illinois 60637

Dear Dr. Sheridan,

All studies, conducted or supported by the Department of Health and Human Services (HHS), which are not otherwise exempt and which propose to involve children as subjects, require Institutional Review Board review in accordance with the provisions of HHS regulations at 45 CFR 46, subpart D. Pursuant to HHS regulations at 45 CFR 46.407, if an IRB reviewing such a protocol does not believe the proposed research meets the requirements of HHS regulations at 45 CFR 46.404, 46.405, or 46.406 **and** finds and documents that the research presents a reasonable opportunity to further the understanding, prevention or alleviation of a serious problem affecting the health or welfare of children, the protocol and supporting materials can be submitted to the Secretary (HHS) for 45 CFR 46.407 consideration.

Attached for your review is the Biological Sciences Division (BSD), Institutional Review Board (IRB) Protocol #13472A, entitled "Gonadotropin Releasing Hormone (GnRH) Agonist Test in Disorders of Puberty." This study receives funding through the General Clinical Research Grant (#MO1RR00055, NIH/NCRR division). The BSD IRB has concluded that a portion of the study qualifies for the review process required under 45 CFR 46.407. On behalf of the BSD IRB, I respectfully request that you forward this research to the Office for Human Research Protections for 407 review consideration.

The purpose of the study is to assess whether hormonal responses to a challenge dose of a gonadotropin releasing hormone agonist (GnRH) can diagnose and distinguish among cases of precocious puberty and delayed puberty. The study will be conducted in the General Clinical Research Center (GCRC). The subject population consists of adults and children who have pubertal disorders, as well as healthy adults and children who will act

as controls. Healthy children will not be less than 7 years old. Children with a disorder can be as young as 6 months (they must weight at least 10 kg and have bone age advancement 2 S.D). A total of 300 evaluable subjects will be enrolled. Study procedures include a physical exam, urine pregnancy test, 2 day (overnight) GCRC stay, sleep testing with blood sampling for overnight LH secretion (through an indwelling intravenous catheter; up to 4 oz), administration of leuprolide acetate through subcutaneous injection and blood sampling (up to 5 oz), bone age radiographs, and blood drawn for DNA testing (up to 2 T). All subjects will be discharged on iron, 300 mg/day, for 1 month to replenish iron. Controls will be compensated $150. Patients will not be compensated. Written consent forms have been provided for each study group, as well as assent forms for children 6 years and older. In regards to funding, the study procedures are carried out in the GCRC which is funded by a grant by the National Institutes of Health. The IRB has on file the portion of the GCRC grant that describes this study. An entire copy of the grant was not requested by the IRB as the entire GCRC grant has already gone review and approval under IRB Protocol #10440.

This study underwent initial review at the Committee A, IRB meeting on November 9, 2004 at which it received Pending-Conditional approval. The study was sent back to Committee A for discussion on January 11, 2005 in order to present the Principal Investigator's response and additional changes that had been requested by the GCRC. At this meeting, the protocol received full approval, except for the portion involving healthy children that will require 407review. The following are key issues that were discussed by the IRB during these meetings:

- **Risk and benefits to children *with* a pubertal disorder:** The assessment of the risk level proved to be challenging as the IRB had to taken into consideration several factors, including the risk associated with administering leuprolide for an un-approved indication, the various other study procedures, and the wide age range of the children. Leuprolide is a long-acting form of gonadotropin releasing hormone and is approved for sustaining puberty, although it is *not* approved for its use in this study as a diagnostic agent. The IRB concluded that the off-label use of leuprolide in and of itself constituted a minor increase over minimal risk in children with a pubertal disorder.

  The IRB concluded that there is the possibility of direct benefit if the study provides a better diagnostic characterization of the child's disorder.

  The IRB agreed that the other study procedures are similar to those that a child with pubertal disorder would undergo during routine clinical treatment; that the risk is justified by the anticipated benefit to the subjects; the relation of the anticipated benefit to the risk is at least as favorable to the subjects as that presented by available alternative approaches; and adequate provisions are made for soliciting the assent of the children and permission of their parents or guardians.

Thus, the IRB found that in children with a pubertal disorder, the research could be approved under 45CFR46.405, (research involving greater than minimal risk but presenting the prospect of direct benefit to the individual subjects).

- **Risks and benefits to healthy children without a pubertal disorder:** Just as in children with pubertal disorders, the IRB concluded that the off-label use of leuprolide constituted a minor increase over minimal risk in healthy children without a pubertal disorder.

  However, in regards to direct benefit, the IRB concluded that there is *no* prospect of direct benefit, and the research is not likely to yield generalizable knowledge about the subject's disorder or condition, since the healthy kids have no disorder. Thus, the research could not be approved under 45 CFR46.404 (minimal risk), 405(greater than minimal risk but there is prospect of direct benefit) or 406 (minor increase over minimal risk, no prospect of direct benefit, but the research is likely to yield generalizable knowledge about the subject's disorder or condition).

  The IRB did agree that this is research not otherwise approvable which presents an opportunity to understand, prevent, or alleviate a serious problem affecting the health or welfare of children. The Committee also found that the research will be conducted in accordance with sound ethical principles; and adequate provisions have been made for soliciting the assent of children and the permission of their parents or guardians. The IRB also found that for healthy children, the permission of both parents must be obtained unless one parent is deceased, unknown, incompetent, or not reasonably available, or when only one parent has legal responsibility for the care custody of the child. Thus, the IRB voted to have the portion of the study involving healthy children without a pubertal disorder undergo review in accordance with 45 CFR46.407.

  For your convenience, the instructions provided by OHRP for submission of materials for review under 45 CFR 46.407 are attached, as well as a copy of all approved protocol documents and relevant correspondences. They are as follows:

  1. Full Approval letter dated 1/11/05
  2. Meeting minutes from 1/11/05
  3. GCRC review dated 12/7/04
  4. Principal Investigator's response to the Pending-Conditional letter
     a. e-mail dated 11/29/04
     b. e-mail dated 12/20/04
     c. e-mail dated 1/5/05
     d. e-mail dated 1/6/05
  5. Pending-Conditional letter dated 11/23/04
  6. Meeting minutes for 11/9/04
  7. The Protocol Submission Form dated 9/7/04
  8. Supplemental Forms A and B (co-investigators and research staff)
  9. Supplemental Form C for research in children (2):
     a. Form C for healthy volunteers

b. Form C for children with a disorder

10. Supplemental Form G for genetic testing
11. The portion of the GCRC grant that describes this study
12. The approved detailed narrative dated 12/15/04
13. The approved written consent forms (4):
    a. Parental consent for child patients dated 1/7/05
    b. Parental consent for child volunteers dated 1/7/05
    c. Adult volunteer consent dated 1/7/05
    d. Adult patient consent dated 1/7/05
14. The approved child assent forms (2):
    a. Volunteer assent dated 11/23/04
    b. Patient assent dated 11/23/04
15. The approved study advertisement dated 10/5/04
16. FDA IND application dated 9/16/04
17. Principal Investigator's response to IRB pre-reviews
18. 2nd IRB pre-review and PI response
19. 1st IRB pre-review and PI response

You may find that only a portion of these documents need to be sent to OHRP. I hope, however, there is enough information provided to be able to understand how the Committee arrived at its final decision. Please feel free to contact me if additional information is required. I look forward to your decision regarding the status of this protocol.

Sincerely,

Jonathan Moss, M.D., Ph.D.
Chairman
Biological Sciences Division, Institutional Review Board