9. The Institutional Review Board meeting minutes dated November 9, 2004.

IRB Meeting Minutes of November 9, 2004

Protocol #: **13472A** – New

Principal Investigator: Robert Rosenfield

Title: Gonadotropin Releasing Hormone (GnRH) Agonist Test in Disorders of Puberty

Summary of protocol: This proposal describes a set of GCRC studies to assess whether hormonal responses to a challenge dose of a gonadotropin releasing hormone agonist (GnRH) can diagnose and distinguish among the cases of precocious puberty and delayed puberty. All subjects will have a 2day (overnight) GCRC stay with blood sampling for overnight LH secretion, normal responses next day to leuprolide acetate through subcutaneous injection, blood drawn for DNA testing, and bone age radiographs. Total blood withdrawn is about ½ pint. All subjects will be discharged on iron, 300 mg/day, for 1 month to replenish iron. Diagnostic specificity and sensitivity of the leuprolide test will be compared with sleep LH levels. Controls will be paid $150. The subject population consists of adults and children who have pubertal disorders, as well as healthy adults and children who will act as controls. A total of 280 evaluable subjects will be enrolled and the PI estimates that 320 individuals will need to be consented in order to obtain 280 evaluable subjects. Healthy children will not be less than 7 years old. Children with disorder can be as young as 6 months. Patients will be recruited by the investigator from his patients at U of C. Healthy volunteers will be recruited by flyers. Written informed consent is necessary. The study will be explained to children at a level they can understand. They will be asked to explain the study in his or her own words back to the person obtaining consent. If they do not wish to participate, their decision will override their parent's decision. Separate consent forms for the parents of healthy kids and kids with a disorder of have been submitted. A consent form for adult subjects has been submitted. Separate assent forms for healthy kids and kids with a disorder have been submitted. The risks of the study procedures include the use of leuprolide which is approved by the FDA for treatment of pubertal disorders. However, its use in this study as a diagnostic agent is considered experimental. The study also involves the placement of an indwelling catheter for 36 hours which could cause irritation. However, the line can be removed during the study if this is preferred by the patient. Up to 1 cup of blood will be drawn during this study. Subjects will be given iron supplement for 1 month after the study is over to replace iron. These risks are also minimized by having the study conducted in the GCRC where there is constant monitoring by GCRC staff and the pediatric endocrinology service is available at any time. There is also the potential for stress from the overnight admission for young children. This stress is minimized by allowing the parents to stay overnight with their child if they wish. In terms of confidentiality, the DNA samples that are collected will be coded. If samples are sent to outside sites, they will not be sent with any identifying information. Any other study data that may be sent outside of U of C, will be deidentified as well.

Discussion:
The Committee discussed if it was appropriate to include children with premature puberty as young as 6 months of age. The PI clarified that for the purposes of this study, premature

puberty is “defined” as onset of puberty as early as 6 months. He will only study infants with premature puberty if they weight at least 10 kg and have bone age advancement 2 S.D. He also noted that infants with premature puberty who meets criteria for “complete precocious puberty” usually have a very serious disorder such as hypothalamic hamartoma or brain tumor that requires a prompt diagnosis and treatment. The standard diagnostic tool is a GnRH test. However, because of its erratic availability, he and other endocrinologists often use leuprolide or Lupron in young infants for diagnostic purposes. He argues that it is best to do this testing where necessary in the context of a monitored GCRC study in infants greater than 10 kg.

The Committee discussed the risk level to children in this study. The Committee took into consideration the P.I.’s experience with administering Leuprolide. However, given that leuprolide is being used in an off-label manner in this study, the Committee concluded that its administration represents a minor increase over minimal risk. In children with a pubertal disorder there might be benefit if the study provides a better diagnostic characterization of their disorder. The Committee also agreed that the study procedures are similar to those that a child with pubertal disorder would undergo during routine clinical treatment. Thus, the Committee 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. 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.

In regards to healthy children, the Committee found that the research represents a minor increase over minimal risk as its use is experimental and there is no definitive data about its effect in healthy kids. The Committee also agreed 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 Committee found that in healthy children, this research must undergo 407 review as it 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.

The Committee discussed if an IND# is needed for the use of leuprolide. It appears that in previous studies, the PI was being provided Lupron from Tap Pharmaceuticals and had an IND# from the FDA for its use in his studies. The PI now states that Tap is no longer providing Lupron and the IND# is “functionally inactive” is he is now using generic leuprolide acetate (not Lupron). The PI also notes that he has sent the FDA an IND annual report informing them of the change to leuprolide acetate. The Committee agreed that the response from the FDA regarding this matter is needed by the IRB.

The Committee discussed the consent forms and agreed that the following changes should be made:

a. On page 2, use lay language to describe "…recently discovered potential regulators and markers of pubertal development when the technology becomes available"
b. On page 3, change "We have performed 457 leuprolide diagnostic tests…" to "We have performed over 400 leuprolide…"
c. On the parental consent forms, add signature lines for both parents
d. On the parental consent form for healthy children, in the "What other options are there?" section, remove "or to have the standard test (with natural GnRH, marketed as Factrel if it is available within a reasonable period of time…)" as they don't need these tests.
e. On the parental consent form for patients and the adult consent form, if parking is being paid for by the study, this should be added to the consent form.

Risk Determination: Minor increase over minimal risk with no benefit to healthy kids; minor increase over minimal risk with direct benefit to kids with a pubertal disorder

Recommendation: Pending Conditional for adults and children with a disorder; 407 review required for healthy children

Approval Period: 1 year
Vote: 12 For 0 Against 0 Abstaining 12 TOTAL
Non-Scientist voting