CLINICAL RESEARCH CENTER

PROTOCOL REVIEW FORM

Reviewer: [redacted]
Investigator: Robert Rosenfield, M.D.
Protocol # 13472

Date assigned: 11/3/04
Date due CRC: 11/16/04
Date to Committee: 11/18/04

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

STATUS OF APPLICATION: [X] new project [ ] renewal

Description of Proposal

This is a merger of two previously approved CRC protocols (#6585 and #9214). The general hypothesis is that hormonal responses to injection of a challenge dose of GnRH agonist (GnRHag) will distinguish, i.e., provide diagnostic discrimination, among disorders of puberty, and that this challenge test will perform as well as the more costly sleep test, which involves frequent blood drawing over a 12-hour period. A total of 240 subjects with incomplete precocity, idiopathic complete precocity, gonadotropin-independent precocious pseudopuberty, gonadotropin deficiency, and constitutional delay of puberty, as well as healthy prepubertal and pubertal controls will be enrolled. Continuous responses will be compared among different groups using analysis of variance. Fifth and 95th percentiles of hormonal responses in controls will be determined, and the sensitivity of the GnRHag test will be estimated by determining the fraction of subjects with values below (above) the 5th (95th) percentile. Sensitivity of the GnRHag and sleep tests will also be compared using McNemar's test.

Strong Points

Distinction among the various types of premature and delayed puberty is difficult, and the sleep test is costly and impractical. The GnRHag challenge test may be a more practical and useful tool to aid in the diagnosis. Although the description of the statistical analyses is at times difficult to follow due to the large number of groups and the nature of the study, the proposed methods are appropriate.

Weak Points

The two previous protocols, #6585 and #9214, date back to 1994 and 1998, yet only 29 of the 240 subjects required have been evaluated to date. Is this a feasible study?

Suggestions for Improvement

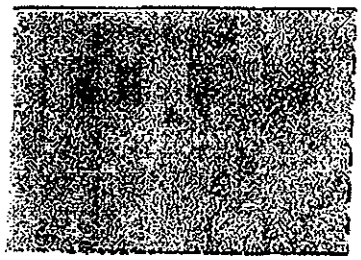
At the end of the Background and Significance section, it might be useful to refer to the sleep test as the "gold standard" test rather than the "major outcome variable for comparisons." Under Comparison of Groups, I believe the intent is to define the 5th percentile as the cutoff for certain tests and the 95th as the cutoff for other tests. Saying that *either* the 5th *or* 95th percentile of the healthy volunteers will define the lower or upper normal limit, depending on the test in question, would help clarify why the specificity is fixed at 95% and not 90%. For the CPP evaluation in 3c), I believe the

cutpoint should be the 95th percentile rather than the stated 5th percentile, since sensitivity is defined as the fraction of CPP patients lying above the cutpoint.

On a minor note, a more suitable response is needed to item 6 in the Data and Safety Monitoring plan. As this is not a therapeutic trial, reference to an intent-to-treat analysis is not appropriate. One could simply say that the dropout rate will be reported but is expected to be low since long-term follow-up is not a part of the study, and that all data obtained prior to dropout will be utilized in the data analyses to the extent possible.

Human subjects/Women & minorities inclusion:	[✓] Adequate	[ ] Inadequate
Justification of subject age range:	[✓] Adequate	[ ] Inadequate
CRC Use/Description of resources:	[✓] Adequate	[ ] Inadequate

Discussed with investigator? [✓] Yes [ ] No (previous versions)



[redacted] 11/12/04

Signature Date