

November 17, 2005

Chair's Summary of the Meeting of the Pediatric Ethics Subcommittee ("407 Panel"), Hilton Gaithersburg Hotel, Gaithersburg MD, November 15, 2005

Presented to the FDA Pediatric Advisory Committee, Hilton Gaithersburg Hotel
November 16, 2005

Proposed Protocol: Gonadotropin Releasing Hormone Agonist Test in Disorders of Puberty

Principal Investigator: Dr Robert Rosenfield, University of Chicago School of Medicine, Department of Pediatrics

Institutional Review Board: IRB #000311, University of Chicago, Biological Sciences Division, School of Medicine

The Pediatric Ethics Subcommittee of the FDA Pediatric Advisory Committee met on November 15, 2005 to review a research proposal entitled "Gonadotropin Releasing Hormone Agonist Test in Disorders of Puberty". The review was requested by the University of Chicago for approval under 45CFR.46.407 and 21CFR50.54. Dr RObert Rosenfield, Principal Investigator, would conduct the proposed study in the General Clinical Research Unit at the University of Chicago Hospitals.

Background

Disorders of puberty are common in American children, including premature onset (precocious puberty) or delayed onset. The medical evaluation of these children, generally done by a pediatric endocrinologist, has been complicated by several factors: (1) availability of gonadotropin releasing hormones – an important component in the medical workup – has been variable; (2) normal values for the currently available product – leuprolide, also known as Lupron - are not available; (3) the gold standard test – a sleep study (collection of blood samples during an overnight hospital stay) – is expensive, not generally reimbursed by third party payers, and thus not used routinely.

The purpose of the proposed protocol is "to establish the diagnostic effectiveness of a (leuprolide) test and the norms for it. This will improve the differential diagnosis of the most common disorders of puberty so that we may provide more accurate and earlier treatment for these disorders."

The proposed study would include two groups: (1) children with disorders of puberty, referred to the investigator in his role as a clinician, for clinical evaluation; (2) healthy children, age 7-18 years, recruited as normal controls to obtain information that would facilitate the interpretation of results in children with disorders of puberty.

Procedures would include a 36-hour admission to the General Clinical Research Unit; insertion of an indwelling venous catheter for obtaining blood samples; total blood sampling of 150-240 cc (5-8 oz); subcutaneous injection of a single dose of leuprolide (10 mcg/kg); x-rays for bone age; banking of DNA obtained from blood samples; and discharge on oral iron to ensure reconstitution of blood.

The enrollment of children in Group 1 is not in dispute. Since they would be exposed to the same tests and procedures that they would have received even if there were no study, the research proposal presents only a minor increase over minimal risk to these children and was approved by the Chicago IRB under 45CFR405: (Research involving greater than minimal risk but presenting the prospect of direct benefit to the individual subjects).

Explanation of the need for 407 review

For simplicity, the following discussion uses the language of Subpart D from HHS regulations at 45CFR46.407. The comparable FDA regulations at 21CFR50.54 are essentially the same, with minor variations.

The University of Chicago concluded that the inclusion of healthy children as normal controls could not be approved outside of the 407 process for the following reasons:

- 45CFR404 refers to protocols of no greater than minimal risk. They concluded that the administration of leuprolide constituted a minor increment over minimal risk and therefore could not be approved under this section.
- 45CFR405 refers to protocols presenting the prospect of direct benefit to the individual subjects. The Committee agreed that the protocol could not be approved under this section since no such prospect exists for the healthy children.
- 45CFR406 refers to protocols involving more than minimal risk and no prospect of direct benefit but likely to yield generalizable knowledge of the subjects' disorder or condition. Since the healthy children do not have a "disorder or condition" the Committee agreed that the protocol could not be approved under this section.
- 45CFR407 refers to "research not otherwise approvable which presents an opportunity to understand, prevent, or alleviate a serious problem affecting the health or welfare of children." Research conducted under this section requires the approval of the Secretary of DHHS. Thus, the request for review.

Public Comments

The Committee received and reviewed eight letters: four from adult patients, one from a parent of a pediatric patient, and three from professional societies.

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The adult patients expressed concerns about: the risk of serious adverse effects from administration of leuprolide, including short term and long term use; hazards for patients and medical personnel from direct contact with leuprolide; charges of misconduct against the TAP corporation, a manufacturer of leuprolide; secrecy surrounding settlements of lawsuits against TAP; the alleged mysterious disappearance of a popular website devoted to victims of leuprolide; and the inadequacy of the consent process in the proposed protocol.

A parent of a child who had cancer and abnormal pubertal development, and who had participated in a clinical trial involving leuprolide, expressed the view that the drug was safe and effective, and stressed the need for better tests to evaluate precocious puberty.

Letters were received from The Endocrine Society, the Lawson Wilkins Pediatric Endocrine Society, and the American Society for Reproductive Medicine. They all stressed the importance of data from normal controls in pediatric research, concerns about the burdens of the 407 process, and concerns about variation among IRB's in the definition of "minimal risk." None of these letters commented on this specific protocol.

Consideration of approval under Section 46.404/50.51 (No Greater Than Minimal Risk)

The Subcommittee reviewed the possibility that the protocol could be approved under section 46.404/50.51 : research involving minimal risk without the prospect of direct benefit. As noted above, the Subcommittee did not consider approval under Sections 405 or 406 because, as the IRB concluded, these did not apply to the healthy children.

There was extensive discussion about the ambiguity and controversy regarding the interpretation of the definition of minimal risk, and the wide variation among IRB's in interpreting this definition, which is stated at 45CFR406.102(i); namely, "Minimal risk means that the probability and magnitude of harm or discomfort anticipated in the research are not greater in and of themselves than those ordinarily encountered in daily life or during the performance of routine physical and psychological examinations or tests."

The subcommittee considered the medical risks of the study, including effects of leuprolide; risks of the procedures, particularly the insertion of an indwelling venous catheter; and the risks of blood loss from the proposed sampling, estimated at 3 cc/kg. The subcommittee also considered the psychological risks of hospitalization for 36 hours in children age 7-18 years, and the psychological risks of the procedures involved.

There was unanimous agreement that these risks were more than minimal, under the federal definition, and the committee therefore agreed with the University of Chicago IRB that the study could not be approved under Section 404.

Consideration of approval under Section 46.407/50.54

Section 407 states:

Sec. 46.407 Research not otherwise approvable which presents an opportunity to understand, prevent, or alleviate a serious problem affecting the health or welfare of children.

HHS will conduct or fund research that the IRB does not believe meets the requirements of Sec. 46.404, Sec. 46.405, or Sec. 46.406 only if:

(a) The IRB finds 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; and
(b) The Secretary (and The Commissioner of FDA), after consultation with a panel of experts in pertinent disciplines (for example: science, medicine, education, ethics, law) and following opportunity for public review and comment, has determined either:

(1) That the research in fact satisfies the conditions of Sec. 46.404, Sec. 46.405, or Sec. 46.406, as applicable, or

(2) The following:

(i) The research presents a reasonable opportunity to further the understanding, prevention, or alleviation of a serious problem affecting the health or welfare of children;

(ii) The research will be conducted in accordance with sound ethical principles;

(iii) Adequate provisions are made for soliciting the assent of children and the permission of their parents or guardians, as set forth in Sec. 46.408.

As noted previously, the subcommittee concluded that the study could not be approved under sections 404, 405, or 406.

The subcommittee therefore considered the following questions:

1. Was the protocol addressing a serious problem affecting the health or welfare of children? There was unanimous agreement that disorders of puberty constituted a serious problem affecting the health and welfare of children. Attention therefore turned to the question of whether the need for improved tests for diagnosis of problems of puberty was a serious problem. A majority (8-1-1) thought that it was. . The minority thought that sufficient data could be obtained from children who were referred for evaluation of concerns about pubertal development, evaluated as part of the patient group (Group 1 above), and who on clinical follow-up were found to be within the normal range. In response, others

stated that these children could not be defined as or presumed to be normal, since they had been referred because of some disorder of pubertal development.

2. Would the research be conducted in accordance with sound ethical principles?

The subcommittee considered several issues under this requirement: the design of the study; the proposal to pay subjects; disclosure of results to normal children; long term storage of samples; and the consent and assent forms.

Design: The subcommittee considered the likelihood of the investigator being able to accrue sufficient subjects to allow for meaningful data to be accumulated. There was credible evidence that the investigator was well along in accumulating data on patients in Group 1 (patients with abnormal pubertal development). With regard to recruitment of healthy controls, the committee agreed with the investigator that his ability to recruit controls could not be tested until he received the necessary approval, not could he enlist the cooperation of investigators from other sites.

Payment: The subcommittee concluded that the proposed payment of \$150, paid by check in the child's for completion of all tests did not constitute an undue inducement. The subcommittee agreed with the proposal to not pay subjects (patients) in Group 1 since the proposed tests were part of their medical care.

Disclosure: Subcommittee members expressed concern about disclosure of results to the normal children or their parents, since the clinical significance of these results would be uncertain and could result in psychosocial harm to the children; e.g., by conveying the false impression that the child was or might be abnormal. Abnormal results could also result in a quest for additional testing or even treatment, with additional risks. There was unanimous agreement that results should not be disclosed to this group. All but one thought this should be a condition of approval; the one thought it should be recommended.

Storage of samples: There was unanimous agreement that the children should be given the opportunity to have their samples destroyed when they reach the age of majority. Seven thought this should be required; two favored a recommendation; one thought the local institutional policy should apply.

Consent and assent. The subcommittee concluded that the forms and procedures for obtaining informed permission from the parents, and assent from the children, were generally satisfactory, with some exceptions. There was unanimous agreement that the consent/assent forms should state more clearly at the beginning that the study was not expected to provide direct medical benefit to the children in the control group, and that suggestions of benefit later in the forms should be removed or revised. There was also agreement that the consent process and forms should mention concerns about adverse effects from long term use of leuprolide. Seven members thought these changes should be a condition of approval; two thought they should be recommendations.. There was also a

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recommendation for assent monitoring of a sample of the healthy children to assure that they understood that they could refuse to participate.

Conclusions

The subcommittee was presented with three options:

1. Recommend to the Pediatric Advisory Committee that the Commissioner/Secretary approve the study as written under Section 46.404/50/51, or under 46.407/50.54. This was unanimously rejected.
2. Recommend to the Pediatric Advisory Committee that the Commissioner/Secretary approve the study under Section 46.407/50.54 with the modifications noted above. This was approved unanimously.
3. Recommend to the Pediatric Advisory Committee that the Commissioner/Secretary disapprove the study. This was implicitly rejected by the vote on #2.

In summary, the Pediatric Ethics Subcommittee of the Pediatric Advisory Committee determined that the proposed research presented a reasonable opportunity to further the understanding of a serious problem affecting the health of children; will be conducted in accordance with sound ethical principles if modified as noted above; and that adequate provisions are made for the soliciting the permission of parents as set forth in 45CFR46.408 and 21CFR50.55, if modified as noted above regarding disclosure of results, storage of samples, and changes to the consent form. . The Subcommittee therefore recommended that the Pediatric Advisory Committee recommend to the FDA Commissioner and the Secretary of DHHS that the research be approved under 45CFR407 and 21CFR50.54 contingent on agreement with the aforementioned modifications.

(signed)

Norman Fost MD MPH
Chair, Pediatric Ethics Subcommittee