THE UNIVERSITY OF CHICAGO

INSTITUTIONAL REVIEW BOARD SUPPLEMENTAL FORM C RESEARCH INVOLVING CHILDREN

Protocol No. ☐☐☐☐☐☐☐

I. BACKGROUND

The ethical mandate of an IRB is to protect the rights and welfare of human research subjects. IRBs are obliged to ensure that research studies do not endanger the safety or well being of human subjects or undermine public confidence in the conduct of research. The special vulnerability of children makes consideration of involving them as research subjects particularly important. To safeguard their interests and to protect them from harm, special ethical and regulatory considerations are in place for reviewing research involving children. Title 45 CFR Part 46, Subpart D provides for "Additional Protection for Children Involved as Subjects of Research." Research that is contrary to the rights and welfare of child subjects is prohibited.

II. IRB CONSIDERATIONS

A. Justification

Please provide written justification that documents the benefits that are likely to accrue to each child participating in the project. The statement should include information gathered on adults if it exists or an explanation about why it does not exist.

Re healthy prepubertal volunteer controls. 1) There are no direct benefits expected for normal volunteers. However, we expect that the results of this study will benefit individuals with pubertal disorders by fulfilling the great need for sex-, age-, and pubertal stage-specific normative data. 2) These studies are of two types: first, multiple blood sampling alone, and second, blood sampling after administration of the test substance leuprolide. The study is potentially beneficial to society by improving diagnostic accuracy fo disorders of puberty. There is a pressing need for sex-, age- and pubertal stage-specific normative data.

The test substance is a GnRHag, a synthetic decapeptide that is identical to natural GnRH (marketed as Factrel®), except that degradation is slower. It is the original type of leuprolide preparation that is marketed to this day as a daily injection for the long-term treatment of precocious puberty in children . In practice, this preparation has been supplanted by the use of a depot preparation (Depo-Lupron®) in a vehicle that slows its absorption to allow monthly injection. Allergic reactions have only been reported to the depot form and are rare (1 case report); they are unheard of in response to a single injection of the short-acting form used for these studies. We have performed 475 leuprolide diagnostic tests in children and adults with no adverse events. There are no known important side effects from a single GnRHag injection other than those related to elevating estrogen to midcycle levels in sexually mature women. The research involves medical risks not unusual for children with premature puberty.

Blood sampling procedures will be performed after the child is admitted to the Clinical Research Center of the University of Chicago Hospitals on a General Pediatric Service with a nurse in constant attendance, a resident in pediatrics available in-house and the Pediatric Endocrinology service on call. Iron stores will be repleted by prescribing Ferrous Sulfate.

Normal volunteers will be reimbursed $100 for undergoing the GnRHag test, $50 for the sleep test.

See Suppl Form C, Patients.

B. Basic Protocol Information

Risk/Benefit Assessment:

Both the FDA and OHRP define **minimal risk** as "a risk where the probability and magnitude of harm or discomfort anticipated in the proposed research are not greater, in and of themselves, than those ordinarily experienced in daily life or during the performance of routine physical or psychological examinations or tests." For example, the risk of drawing a small amount of blood from a healthy individual for research purposes is no greater than the risk of doing so as part of a routine physical examination.

In your opinion, the research presents (check one and follow the applicable instructions):

☐ No greater than minimal risk to the subject. ***(Complete Section C.)***

☐ Greater than minimal risk but presents the prospect of a direct benefit to the subjects. ***(Complete Section D.)***

☒ Greater than minimal risk with no prospect of a direct benefit to the subjects but likely to yield generalizable knowledge about the subject's disorder or condition. ***(Complete Section E).***

C. Research Involving No More Than Minimal Risk

Consent and/or Assent of Subject Participation:

1) Are you requesting waiver of consent? ☐ Yes ☐ No

If yes, please indicate that you have provided the IRB with **one** of the following:

☐ written justification of waiver for **each** of the four regulatory requirements (see page 15 of the submission form); or

☐ written documentation indicating to the IRB that the research protocol is designed for conditions or for a subject population for which parental or guardian permission is not a reasonable requirement to protect the subjects (i.e., abused or neglected children). Additional mechanisms for protecting the subject have been substituted.

2) If a waiver of consent is not being requested:

(a) Does the consent form include provisions for parental/guardian consent?

☐ Yes ☐ No*

*Please include a provision for consent of at least one parent or guardian.

(b) Does the consent form include provisions for assent of the subject?

☐ Yes ☐ No**

If "no" and the age, maturity and psychological state of the children renders them fully capable of assenting, the IRB requires that an explanation be given for not securing the assent of the children (in the state of Illinois, the age of 7 is commonly believed to be the age at which a child gains capacity to assent). In circumstances where the subject is fully capable of assenting, the IRB will waive the assent of the child only if (i) the intervention or procedure involved holds out the prospect of direct benefit that is important to the health or well-being of the child **and (ii) this direct benefit is available only in the context of the research.

D. Research Involving Greater than Minimal Risk But Presenting the Prospect of Direct Benefit to Subjects

1) Have the direct benefits been described in the submission form, protocol, and consent form?

☐ Yes ☐ No*

2) Are the anticipated risks justified by the anticipated benefits to the subjects?

☐ Yes ☐ No*

3) Is the anticipated risk/benefit ratio at least as favorable to the subjects as that presented by available alternative approaches?

☐ Yes ☐ No*

*If "no" to **any** of the above risk assessment questions, the IRB may be prohibited from approving the study.

Consent and/or Assent of Subject Participation:

1) Are you requesting waiver of consent? ☐ Yes* ☐ No

*Note: The IRB requires written documentation indicating to the IRB that the research protocol is designed for conditions or a subject population for which parental or guardian permission is not reasonable requirements to protect the subjects (example: neglected or abused children). Additional mechanisms for protecting the subjects have been substituted.

2) If a waiver of consent is not being requested:

(a) Does the consent form include provisions for parental/guardian consent?

☐ Yes ☐ No*

*Please include a provision for consent of at least one parent or guardian.

(b) Does the consent form include provisions for assent of the subject?

☐ Yes ☐ No**

If "no" and the age, maturity and psychological state of the children renders them fully capable of assenting, the IRB requires that an explanation be given for not securing the assent of the children (In the state of Illinois, the age of 7 is commonly believed to be the age at which a child gains capacity to assent). In circumstances where the subject is fully capable of assenting, the IRB will waive the assent of the child only if (i) the intervention or procedure involved holds out the prospect of direct benefit that is important to the health or well-being of the child **and (ii) this direct benefit is available only in the context of the research.

E. Research Involving Greater Than Minimal Risk With No Prospect of Direct Benefit to Subjects But Likely to Yield Generalizable Knowledge About the Subject's Disorder or Condition

1) Does the risk represent a minor increase over minimal risk?

☒ Yes ☐ No*

2) Does the intervention or procedure present experiences to subjects that are reasonable and commensurate with those inherent in their actual or expected medical, dental, psychological, social, or education situations?

☐ Yes ☒ No*

3) Is the generalizable knowledge yielded by the intervention or procedure of great vital importance for the understanding or amelioration of the subjects' disorder or condition?

☐ Yes ☒ No*

*If "no" to **any** of the above risk assessment questions, the IRB may be prohibited from approving the study.

Consent and/or Assent of Subject Participation:

1) Are you requesting waiver of consent? ☐ Yes* ☒ No

*Note: The IRB requires written documentation indicating to the IRB that the research protocol is designed for conditions or a subject population for which parental or guardian permission is not reasonable requirements to protect the subjects (example: neglected or abused children). Additional mechanisms for protecting the subjects have been substituted.

2) If a waiver of consent is not being requested:

(a) Does the consent form include provisions for parental/guardian consent?

☒ Yes ☐ No*

*If no, please include a provision for consent of **both** parents unless one parent is deceased, unknown, or not reasonably available, or when one parent has legal responsibility for the care and custody of the child.

(b) Does the consent form include provisions for assent of the subject?

☒ Yes ☐ No**

If "no" and the age, maturity and psychological state of the children renders them fully capable of assenting, the IRB requires that an explanation be given for not securing the assent of the children (in the state of Illinois, the age of 7 is commonly believed to be the age at which a child gains capacity to assent). In circumstances where the subject is fully capable of assenting, the IRB will waive the assent of the child only if (i) the intervention or procedure involved holds out the prospect of direct benefit that is important to the health or well-being of the child **and (ii) this direct benefit is available only in the context of the research.