INFORMED CONSENT

Are you participating in any other research studies? _____ yes  _____ no

INTRODUCTION TO RESEARCH STUDIES

A research study is designed to answer specific questions, sometimes about a drug or device’s safety and its effectiveness. Being in a research study is different from being a patient. When you are a patient, you and your personal doctor have a great deal of freedom in making decisions about your health care. When you are a research subject, the Protocol Director and the research staff will follow the rules of the research study (protocol) as closely as possible, without compromising your health.

PURPOSE OF RESEARCH

Your child is invited to participate in a research study of Depot Leuprolide (DL) for the treatment of central precocious puberty (CPP). We hope to learn the minimal effective dose of DL that will serve to delay precocious development and whether the monthly injections of DL and newer 3 and 4 month injection dose amounts of DL are completely equivalent in stopping puberty. Different monthly DL doses and the 11.25, 22.5, and 30 mg multi-month versions have been found effective in stopping the progression of puberty, but we need to better understand by directly comparing them whether there are any long term differences in effectiveness. Your child was selected as a possible participant in this study because he/she is about to commence or is currently on DL therapy for clinical reasons that your doctors have discussed with you. Stanford University expects to enroll 110 children over many years.

Your child’s participation in this study is entirely voluntary.

Your decision whether or not to participate will not prejudice your child’s medical care. If you decide to participate, you are free to withdraw your consent, and to discontinue participation at any time without prejudice to your child or effect on your child’s medical care. If you decide to withdraw from this research, please tell your study doctor. There are no anticipated consequences to withdrawal from the research study. Your child’s
continuation on Depot Leuprolide therapy will be based on clinical indications, regardless of his/her participation in the study. To terminate participation simply inform your research doctor at your child's scheduled clinic visit or call Dr. Kirk Neely at 650-723-5791.

**DURATION OF STUDY INVOLVEMENT**

This research study has different sub-studies and is expected to take approximately 10 years. Each patient will be on DL for 2 or more years depending entirely upon the clinical indication. After DL is discontinued, the patient will be followed in clinic for a year or more to assure that puberty proceeds normally.

**PROCEDURES**

If your child is newly diagnosed with precocious puberty and you decide to participate in the study, we will randomly assign your child to either the 22.5 or 30 mg multi-month DL injection.

In keeping with our usual clinical practice your child will receive DL injections in our pediatric endocrine clinic. Our experienced endocrine nurses will administer injections. A full clinical evaluation will be performed by a doctor every 3 or 4 months during the first year of therapy and then usually every 6 months, as is standard in clinical practice. At these visits a blood test will be performed 40 minutes after DL administration to assess for continued hormonal suppression. Alternatively, an injection of short-acting leuprolide may be used to stimulate hormone release as a test of hormone suppression. Approximately half a teaspoon of blood will be taken. Children who show clinical advance of puberty will be given the monthly DL or an annual implant if necessary. No extra visits will be needed, as evaluations will occur at scheduled routine clinic appointments for the DL shots. A bone age X-ray will be obtained at the beginning of the study and then every year, as is routinely done in assessing the degree of precocious puberty and its treatment.

You will be told if any new information is learned which may affect your child's condition or influence your willingness to continue participation in this study.
Tissue Sampling or Banking For Research

Research using blood is an important way to try to understand human disease. You have been given this consent form because the investigators want to include your child’s blood in this research project. They also want to save his/her blood so that they can measure his/her hormone levels at a later date.

There are several things you should know before allowing your child’s blood to be studied:

Your child’s blood will be stored under his/her name.

Your child’s name or other public identifiers will not be included with any data shared with other investigators.

Knowing your child's results will pose no risk to you or your child.

You will be told the results of all your child’s blood tests.

You have the right to refuse to allow your child’s blood to be studied now or saved for future study. You may withdraw from this study at any time. The investigators might retain the identified samples, e.g., as part of your routine clinical care, but not for additional research.

SUBJECT’S RESPONSIBILITIES

You should:

- Keep your study appointments. If it is necessary to miss an appointment, please contact the Protocol Director or research study staff to reschedule as soon as you know you will miss the appointment.
- Tell the Protocol Director or research study staff about any side effects, doctor visits, or hospitalizations that you may have.
- Ask questions as you think of them.
Tell the Protocol Director or research staff if you change your mind about staying in the study.

While participating in this study, your child should not take part in any other research project without approval from all of the investigators. This is to protect your child from possible injury arising from such things as extra blood drawing, extra x-rays, interaction of research drugs, or similar hazards.

WITHDRAWAL FROM STUDY

If you first agree to participate and then you change your mind, you are free to withdraw your consent and discontinue your participation at any time. Your decision will not affect your ability to receive medical care for your disease and you will not lose any benefits to which you would otherwise be entitled.

At the discretion of the protocol director subjects may be taken out of this study due to unanticipated circumstances. Some possible reasons for withdrawing a subject from the study are:

- skin reactions to injections
- failure to follow instructions
- the investigator decides that continuation could be harmful to you
- you need treatment not allowed in the study
- the study is canceled
- other administrative reasons

POSSIBLE RISKS, DISCOMFORTS, AND INCONVENIENCES

There are risks, discomforts, and inconveniences associated with any research study. These deserve careful thought. You should talk with the Protocol Director if you have any questions.

All current patients on DL therapy and newly diagnosed children with PP commencing DL will be invited to participate in our study. Your child will be receiving DL for clinical indications and therefore the minor risks of this drug would be present without this
study. Risks include pain, bruising, and sterile abscess formation at the site of injection. These local reactions occur in approximately 5% of patients. Also pain, swelling and bruising may occur at the site where blood is drawn. Again, monitoring for treatment adequacy through blood testing represents routine clinical care for patients on treatment for CPP. These discomforts are usually minor, temporary and in our experience, pain can be decreased when EMLA cream is used. EMLA cream is offered routinely to all children prior to DL administration and blood testing.

Pubertal progression on the lower dose or 3 or 4 month DL would be another potential risk.

Participation in this study may involve risks to your child which are currently unforeseeable.

**POTENTIAL BENEFITS**

Potential benefits of this study include information that would allow us to routinely use lower doses of DL or the 3 or 4 month injection of DL in the treatment of early puberty. By using lower or less frequent doses we can reduce the potential for side-effects and make treatment more convenient.

**WE CANNOT AND DO NOT GUARANTEE OR PROMISE THAT YOUR CHILD WILL RECEIVE ANY BENEFITS FROM THIS STUDY**

**ALTERNATIVES**

The alternative is not to participate. If you choose not to participate in the study, your child will continue to receive the same care that he/she would ordinarily receive.

**SUBJECT’S RIGHTS**

You should not feel obligated to agree to participate. Your questions should be answered clearly and to your satisfaction.

If you decide not to participate, tell the Protocol Director. You will still receive care for your disease and will not lose any benefits to which you would otherwise be entitled.
You will be told of any important new information that is learned during the course of this research study, which might affect your condition or your willingness to continue participation in this study.

**CONFIDENTIALITY**

Your identity will be kept as confidential as possible as required by law. Except as required by law, you will not be identified by name, social security number, address, telephone number, or any other direct personal identifier. Your research records may be disclosed outside of Stanford, but in this case, you will be identified only by a unique code number. Information about the code will be kept in a secure location and access limited to research study personnel.

The results of this research study may be presented at scientific or medical meetings or published in scientific journals. However, your identity will not be disclosed.

Patient information may be provided to Federal and other regulatory agencies as required. The Food and Drug Administration (FDA), for example, may inspect research records and learn your identity if this study falls within its jurisdiction.

Any data that may be published in scientific journals will not reveal the identity of the subjects. Patient information may be provided to Federal and regulatory agencies as required. The Food and Drug Administration, for example, may inspect research records and learn your identity if this study falls within its jurisdiction.
USE AND DISCLOSURE OF YOUR MEDICAL INFORMATION

Because information about you and your health is personal and private, it generally cannot be used in this research study without your written authorization. If you sign this form, it will provide that authorization. The form is intended to inform you about how your health information will be used or disclosed in the study. Your information will only be used in accordance with this authorization form and the informed consent form and as required or allowed by law. Please read it carefully before signing it.

What is the purpose of this research study and how will my health information be utilized in the study?

We hope to learn the minimal effective dose of DL that will serve to delay precocious development and whether the standard monthly injections of DL and the newer 3 or 4 month injection of DL are completely equivalent in stopping puberty. Your information in some form will be submitted to the FDA.

Do I have to sign this authorization form?

You do not have to sign this authorization form. But if you do not, you will not be able to participate in this research study including receiving any research-related treatment. Signing the form is not a condition for receiving any medical care outside the study.

If I sign, can I revoke it or withdraw from the research later?

If you decide to participate, you are free to withdraw your authorization regarding the use and disclosure of your health information (and to discontinue any other participation in the study) at any time. After any revocation, your health information will no longer be used or disclosed in the study, except to the extent that the law allows us to continue using your information (e.g., necessary to maintain integrity of research). If you wish
to revoke your authorization for the research use or disclosure of your health information in this study, you must contact: Dr. Neely or Wilson at 650 723 5791.

**What Information Will Be Used or Disclosed?**

Your child’s health information related to this study, including, but not limited to physical examination and hormone measurements may be used or disclosed in connection with this research study.

**Who May Use or Disclose the Information?**

The following parties are authorized to use and/or disclose your child’s health information in connection with this research study:

- The Protocol Director- E. Kirk Neely MD
- The Stanford University Administrative Panel on Human Subjects in Medical Research and any other unit of Stanford University as necessary.
- Other study investigators

**Who May Receive / Use the Information?**

The parties listed in the preceding paragraph may disclose your child’s health information to the following persons and organizations for their use in connection with this research study:

- The Office for Human Research Protections in the U.S. Department of Health and Human Services
- Collaborators at other institutions
- The Food and Drug Administration

Your information may be redisclosed if the recipients described above are
not required by law to protect the privacy of the information.

**Expiration**

Your authorization for the use and/or disclosure of your child’s health information will expire on February 8, 2030.

**When Access to Your Information May Be Limited**

You may not be allowed to see or copy certain information in your child’s medical records collected in connection with your child’s participation in this research study while the research is in progress.

________________________________
Signature of Subject

________________________________
Signature of Legally Authorized Representative

______________
Date

________________________________
Description of Representative’s Authority to Act for Subject
FINANCIAL CONSIDERATIONS

PAYMENT

No payment will be provided for participation in this project.

COSTS

You will continue to be responsible for the costs of clinical care. There will be no extra cost to you for your child’s participation in this study.

SPONSOR

No companies or institutions are providing support and/or materials for this study.

CONSULTATIVE OR FINANCIAL RELATIONSHIPS

Dr. Neely serves as a paid advisor to Abbott, which makes Depot Lupron.

CONTACT INFORMATION

If you have any questions, concerns or complaints about this research study, its procedures, risks and benefits, or alternative courses of treatment, you should ask the Protocol Director, Dr. Kirk Neely at 650-723-5791 or Eileen Durham RN, Dr. Kim Fuld or Dr. Darrell Wilson.

If you feel you have been hurt by being a part of this study, please contact the Protocol Director Dr. Kirk Neely at 650-723-5791 or Eileen Durham RN, Dr. Kim Fuld or Dr. Darrell Wilson.

If you are not satisfied with how this study is being conducted, or if you have any concerns, complaints, or general questions about the research or your rights as a participant, please contact the Stanford Institutional Review Board (IRB) to speak to someone independent of the research team at (650)-723-5244 or toll free at 1-866-680-2906. You can also write to the Stanford IRB, Stanford University, Stanford, CA 94305-5401.
COMPENSATION

All forms of medical diagnosis and treatment -- whether routine or experimental -- involve some risk of injury. In spite of all precautions, you might develop medical complications from participating in this study. If such complications arise, the researchers will assist you in obtaining appropriate medical treatment but this study does not provide financial assistance for additional medical or other costs. (Additionally Stanford is not responsible for research and medical care by other institutions or personnel participating in this study.) You do not waive any liability rights for personal injury by signing this form.

EXPERIMENTAL SUBJECT’S BILL OF RIGHTS

As a human subject you have the following rights. These rights include but are not limited to the subject’s right to:

• be informed of the nature and purpose of the experiment;
• be given an explanation of the procedures to be followed in the medical experiment, and any drug or device to be utilized;
• be given a description of any attendant discomforts and risks reasonably to be expected;
• be given an explanation of any benefits to the subject reasonably to be expected, if applicable;
• be given a disclosure of any appropriate alternatives, drugs or devices that might be advantageous to the subject, their relative risks and benefits;
• be informed of the avenues of medical treatment, if any available to the subject after the experiment if complications should rise;
• be given an opportunity to ask questions concerning the experiment or the procedures involved;
• be instructed that consent to participate in the medical experiment may be withdrawn at any time and the subject may discontinue participation without prejudice;
• be given a copy of the signed and dated consent form;
• and be given the opportunity to decide to consent or not to consent to a medical experiment without the intervention of any element of force, fraud, deceit,
duress, coercion or undue influence on the subject's decision.

YOUR SIGNATURE INDICATES THAT YOU HAVE READ AND UNDERSTAND THE ABOVE INFORMATION, THAT YOU HAVE DISCUSSED THIS STUDY WITH THE PERSON OBTAINING CONSENT, THAT YOU HAVE DECIDED THAT YOUR CHILD WILL PARTICIPATE BASED ON THE INFORMATION PROVIDED, AND THAT A COPY OF THIS FORM HAS BEEN GIVEN TO YOU.

Signature of LAR (Parent, Guardian or Conservator) Date

Authority to act for participant

(If available) Signature of Other Parent or Guardian Date

Authority to act for participant

The IRB determined that the permission of two parents is required for research to be conducted under 45 CFR 46.405, in accordance with 45 CFR 46.408(b) unless one parent is deceased, unknown, incompetent, not reasonably available, or only one parent has legal responsibility for the care and custody of the child. Not reasonably available means that the other parent is not present during the consenting process, or will not be available prior to the start of research procedures.

*Person Obtaining Consent
I attest that the requirements for informed consent for the medical research project described in this form have been satisfied - that the subject has been provided with the Experimental Subject’s Bill of Rights, if appropriate, that I have discussed the research project with the subject and explained to him or her in non-technical terms all of the information contained in this informed consent form, including any risks and adverse reactions that may reasonably be expected to occur. I further certify that I encouraged the subject to ask questions and that all questions asked were answered.

Signature of Person Obtaining Consent

Date