The UNIVERSITY OF CHICAGO
The Division of the Biological Sciences • The University of Chicago Hospitals

CONSENT BY SUBJECT FOR PARTICIPATION IN A RESEARCH PROTOCOL

Protocol Number: 13472A Name of Subject: _____
Medical History Number: _____

STUDY TITLE: **Gonadotropin Releasing Hormone (GnRH) Agonist Test in Disorders of Puberty. (Patients)**

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Your child is being asked to participate in a research study. A member of the research team will explain what is involved in this study and how it will affect your child. This consent form describes the study procedures, the risks and benefits of participation, as well as how your child's confidentiality will be maintained. Please take your time to ask questions and feel comfortable making a decision whether to participate or not. This process is called informed consent. If you decide to have your child participate in this study, you will be asked to sign this form.

WHY IS THIS STUDY BEING DONE?
Your child is being asked to participate in a research study to test the effectiveness of the drug, leuprolide, in finding the causes of various disorders of puberty. Leuprolide is a man-made form of gonadotropin releasing hormone (GnRH) that starts puberty. Pilot studies show evidence that it may be better for testing than the natural hormone. This drug is considered experimental for this purpose because, although it is widely prescribed for the long-term treatment of hormone imbalances in children and adults, it is not advertised by the pharmaceutical companies to be used as a diagnostic test.

HOW MANY PEOPLE WILL TAKE PART IN THE STUDY?
About 280 people will take part in this study at the University of Chicago.

WHAT IS INVOLVED IN THE STUDY?
Your child will be admitted to the Clinical Research Center (CRC), a special patient floor where only research studies are done, at the University of Chicago Hospitals at approximately noon on the first day of the study, where he or she will have:

- a physical examination,
- an x-ray of the left hand and wrist to determine bone age,
- a sleep test, and
- a leuprolide test starting the next morning.

Your child will be discharged 24 hours after the leuprolide test begins.

Sleep testing begins at approximately 7 pm that evening, after the CRC staff inserts an ordinary intravenous (IV) line (a small tube placed in the arm vein using a needle) so that we can get blood samples with as few needle sticks as possible. We will keep the IV line from clotting (gelling of the blood that forms clots) by filling it with a medication (heparin) which prevents blood clotting. The test involves automatically drawing blood every 20 minutes through the IV line with a small pump for 12 hours overnight to measure the amount of gonadotropins (LH and FSH, the hormones that stimulate the testicles in men and ovaries in women to make sex hormones) and sex hormones made during sleep. This helps to find out whether true puberty (maturing of sex organs) has begun because production of gonadotropins and sex hormones begin during sleep. Less than four ounces (1/2 cup) of blood will be taken for this test (8 tablespoons at most).

Leuprolide is a man-made form of the hormone (GnRH) that naturally starts puberty by stimulating the pituitary gland (a gland in the brain that regulates hormones) to make gonadotropins (LH and FSH, the hormones that stimulate the testicles and ovaries). Leuprolide is stronger and longer-acting than natural GnRH. Leuprolide is given to test how well your child's pituitary gland controls the function of his or her testicles or ovaries. It normally causes the pituitary gland to stimulate the testicles or ovaries to make sex hormones for one or two days. Leuprolide is widely prescribed for the long-term treatment of a many hormone imbalances in children and adults. Leuprolide is not advertised by the pharmaceutical companies to be used as a diagnostic test.

The leuprolide test will start at about 7:00 AM with blood drawing through the IV line previously inserted, unless the line has unexpectedly been dislodged or clotted. Leuprolide will be given as a single injection under the skin. Up to 12 blood samples (each 3 to 20 ml, which is 0.5 to 4 tsp) will be taken for 1 hour before and for 24 hours after the injection to measure gonadotropins (LH and FSH, hormones which stimulate the testicles and ovaries), sex hormone levels, and recently discovered substances that may control and show the progression of puberty. These recently discovered substances (such as activin, inhibin and free alpha subunit) will be measured when tests for them become available. About five ounces of blood (a little over a half cup) will be taken for this group of tests. You will then be discharged from the Clinical Research Center.

_____*I do not wish for my child's blood samples to be sent to other centers for assay of new markers of puberty.*

_____*I give my permission for my child's blood samples to be sent to other centers for assay of new markers of puberty.*

DNA sample: With your permission, two additional tablespoons of blood will be drawn for future studies of the genetic cause of delayed puberty. In order to conduct such studies, we will extract DNA from the blood and store it in deep freeze in the CRC Core Laboratory. It is possible that a sample of your child's DNA might be sent to another researcher for further testing for this purpose. To protect your child's identity, his or her DNA samples will be identified only by a code. We will also use some of the blood to create a cell line. A cell line is a way of preserving the cells in your blood so that they can be reproduced and kept around for as long as we need them. If we should run out of the DNA extracted from your blood, we will use the cell line as a back-up source and create more DNA from it. That way, we do not need to draw more blood from your child if more DNA is required and if new technology for future genetic analysis eventually becomes available. We intend to use the cell lines strictly for studies regarding the genetic cause of abnormal puberty. The cell line will be owned by the University of Chicago. Any information or products that are derived from these cell lines will be the

property of the University of Chicago, but will not be used for anything but the designated studies without your explicit consent. Please initial one of the following options regarding our taking a blood sample to obtain DNA for this purpose.

_____ *I do not wish my child to give blood for DNA and cell line creation*
_____ *I give my permission to take my child's blood for DNA and cell line creation*

During this study, Dr. Rosenfield and his research team will collect information about your child for the purposes of this research, including name, address, telephone number, e-mail address, social security number and medical record number, parent names and addresses, medical history and examination findings, results of the bone age film, and the results of the sleep and GnRH agonist (Leuprolide) tests.

HOW LONG WILL I BE IN THE STUDY?

Your child will be scheduled for admission in the early afternoon. The study is scheduled to start in the early evening that day and finish early morning 2 days later (for a total of about 36 hours).

Dr. Rosenfield may decide to take your child off of the study without your consent if your child is unable to meet the requirements of the study, his or her medical condition changes, the study drug is no longer available, new information becomes available that indicates that participation in this study is not in his or her best interest, or if the study is stopped.

WHAT ARE THE RISKS OF THE STUDY?

- The needle is ordinarily left in place for 36 hours and may cause irritation or bruising at the insertion site, redness or swelling of the vein, or infection. Precautions will be taken to prevent this. The intravenous line may be removed during part of this time if that is the child's preference or if there are access limitations; removal of the line is more common in younger children.
- The amount of blood taken is equal to less than a cup (8 ounces) total. This amount of blood is ordinarily not enough to cause a low blood count. Although the amount of blood drawn is not dangerous, it may be enough to cause temporary dizziness. Precautions will be taken to prevent this. We also ask that your child take a multivitamin with iron for one month after the study to assist his or her body in replacing the blood that we take during the study. Side effects from iron may include constipation, dark stools and possible stomach irritation.
- Heparin is used to prevent clotting in the IV tubing. The amount of heparin used is too little to cause excessive bleeding from the vein.
- Anxiety symptoms may occur related to the needle sticks required to draw blood samples. These include numbness or tingling of the hands or feet, and constipation.
- Leuprolide has no known direct or permanent side effects. In adult women the changes in hormones may cause temporary premenstrual-type symptoms and/or delay ovulation by about a week after the test is performed. Premenstrual symptoms include nausea, breast tenderness, and mood swings. Delayed ovulation can delay the onset of the next period. Leuprolide is mixed in a preservative called benzyl alcohol to which some people are allergic. The hormone changes that result from long-term use (over 6 months) can cause thinning of the bones (osteoporosis). Allergic reactions vary from one person to another and may include redness, rashes, and swelling.
- Leuprolide has been used for the treatment of hundreds, if not thousands, of children. It is widely used for the treatment of otherwise healthy children who are short in height and have early puberty. We have also performed over 400 leuprolide diagnostic tests in children,

including a small number of healthy volunteer children, and adults. In all these situations, there are no known short- or long-term direct side effects.

- Unforeseeable side effects or adverse reactions, such as allergic reactions could occur. A severe allergic reaction has been reported after man-made GnRH was given in a patient born with absence of the hormone. Your child will be closely watched to avoid complications.
- People may find out your child participate in this study and the results of his or her tests. It is important to us that this not happen. DNA samples are identified only by code with the ID number linking the sample to your child being kept under lock and key in the Clinical Research Center and the offices of Dr. Rosenfield; only the research staff will have access to the records.

ARE THERE ANY BENEFITS TO TAKING PART IN THE STUDY?
Your child may benefit from the possible detection of certain sex hormone imbalances. We hope the information learned from this study will benefit other individuals with similar disorders in the future.

WHAT OTHER OPTIONS ARE THERE?
Participation is voluntary. You may choose not to allow your child to undergo these tests or to have the standard test (with natural GnRH, marketed as Factrel®) if it is available within a reasonable period of time, or with GnRH agonist (leuprolide) test performed commercially.

The decision whether or not you wish your child to participate in this study will not affect his or her care at the University of Chicago Hospitals.

WHAT ARE THE COSTS?
There will be no cost to you.

In the event of physical injury resulting from this research, if emergency care is needed the University of Chicago Hospitals will provide it to your child free of charge. If non-emergency care is necessary, the University of Chicago Hospitals will provide it to your child at your cost. Except for such emergency care, the University of Chicago Hospitals and the University of Chicago do not provide free medical care or payment to you.

WILL I BE PAID FOR MY PARTICIPATION?
Patients will not be paid for participating.

WHAT ABOUT CONFIDENTIALITY?
Study records that identify your child will be kept confidential. To protect your child's identity, his or her blood samples and test results will be identified only by ID number for analysis. The record linking the ID number to your child's identity will be kept under lock and key in the Clinical Research Center and the offices of Dr. Rosenfield, and only he and his research staff will have access to this record. Your child's research records will be collected and maintained as computer files and as paper files indefinitely, and only research staff will have access to them.

The data collected in this study will be used for the purpose described in the form. By signing this form, you are allowing the research team access to your child's medical records, which include Protected Health Information. Protected Health Information (PHI) includes any health information that is collected about your child, which could include your child's medical history and new information

collected from this study. The research team includes the individuals listed on this consent form and other employees involved in this study at the University of Chicago.

Your child's blood samples and DNA may be sent to outside laboratories when the technology is more advanced for hormone and genetic testing not available at the University of Chicago. However, to protect your child's identity, these blood samples and test results will be identified only by ID number.

As part of the study, Dr. Rosenfield and his research team will anonymously report the results of your study-related procedures and tests explained above to the National Institutes of Health (NIH). These would include all test and all other elements of protected health information, as outlined above. This information is being sent because progress reports are required for ongoing funding of the study by the NIH.

Your child's records may be reviewed by federal agencies who are responsible for protecting human subjects in research including the Food and Drug Administration (FDA) and Office of Human Research Protections (OHRP). In addition, representatives of the University of Chicago, including the Institutional Review Board, a committee that oversees the research at the University of Chicago, may also review the records from the research. If your research record is reviewed by any of these groups, they may also need to review your entire medical record.

The results from tests and/or procedures performed as part of this study will become part of your child's medical record. Copies of your child's medical record can be obtained by requesting your child's medical record from the Medical Records Department. Dr. Rosenfield will inform you in writing of your child's results from the study.

During your child's participation in this study, you will have access to his or her medical record. Dr. Rosenfield is not required to release to you research information that is not part of your child's medical record.

The study results will be kept in your child's research record and be used by the research team indefinitely. Any research information in your child's medical record will be kept indefinitely.

Data from this study may be used in medical publications or presentations. Your child's name and other identifying information will be removed before this data is used. If we wish to use identifying information in publications, we will ask for your approval at that time.

WHAT ARE MY RIGHTS AS A PARTICIPANT?

Participating in this study is voluntary. If you choose not to have your child participate in this study, his or her care at the University of Chicago/University of Chicago Hospitals will not be affected.

You may choose to have your child stop participating at any time during the study. Leaving the study will not affect his or her care at the University of Chicago/University of Chicago Hospitals.

If you choose not to have your child in the study any longer and you do not want any of your child's future health information to be used, you must inform Dr. Rosenfield in writing at the address on the

first page. Dr. Rosenfield may still use the information that was collected about your child prior to your written notice.

We will tell you about significant new information that may affect your willingness to have your child stay in this study.

You will be given a signed copy of this document.

WHO DO I CALL IF I HAVE QUESTIONS OR PROBLEMS?
You have talked to _____about this study and you had the opportunity to ask questions concerning any and all aspects of the research. If you have further questions about the study, you may call Dr. Rosenfield at 773-702-6432.

If your child has a research related injury, you should immediately contact the Pediatric Endocrinologist on call at 773-702-6800, pager 9296.

If you have any questions concerning your rights in this research study you may contact the Institutional Review Board, which is concerned with the protection of subjects in research projects. You may reach the Committee office between 8:30 am and 5:00 pm, Monday through Friday, by calling (773) 702-6505 or by writing: Institutional Review Board, University of Chicago, 5841 S. Maryland Avenue, MC 1108, Chicago, Illinois 60637.

CONSENT

The research project and the procedures associated with it have been explained to me. The experimental procedures have been identified and no guarantee has been given about the possible results. I have received a signed copy of this consent form for my records.

PARENT/GUARDIAN/ OR LEGALLY AUTHORIZED REPRESENTATIVE:
I give my permission for my child/relative to participate in the above described research project.

Signature of Parent/Guardian/ or Legally Authorized Representative: _____
Date: _____ Time: _____ AM/PM (Circle)

PERSON OBTAINING CONSENT
I have explained to _____the nature and purpose of the study and the risks involved. I have answered and will answer all questions to the best of my ability. I have given a signed copy of the consent form to the subject.

Signature of Person Obtaining Consent: _____
Date: _____ Time: _____ AM/PM (Circle)

INVESTIGATOR/PHYSICIAN:

Signature of Investigator/Physician _____
Date: _____ Time: _____ AM/PM (Circle)