Please check all that are applicable:

☐ I am an adult participant in this study.

Print your name here: _____

☐ I am the parent or guardian granting permission for a child in this study

Print child's name here: _____

(The use of "you" refers to "your child" or "your ward" or the adult participant)

Is your child 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's or device's safety and effectiveness. Being in a research study is different from being a patient. When you are a patient, you and your doctor have a great deal of freedom in making decisions about your health care. When you are a research participant, 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 son was selected as a possible participant in this study because he is smaller than we would expect for your family and we think that these medications may help him grow for a longer period of time and possibly make him taller than he otherwise would be.

Aromatase inhibitors are a class of medication that blocks the conversion of testosterone to estrogen. Estrogen actually fuses the growth plates for both boys and girls. So, if we can decrease the amount of estrogen your son's body can make, we can delay the fusion of his growth plates, giving him a longer time to grow. There have been several other studies looking at the medications we will be using that have all been very promising for improvement of height. However, not all the studies have been completed to adult height.

Your participation in this study is entirely voluntary.

Your decision whether or not to participate will not prejudice your child or his medical care. If you decide to participate, you are free to withdraw your consent, *a*nd to discontinue participation at any time without prejudice to your son or effect on his medical care. If you decide to terminate your participation in this study, you should notify Dr. Kirk Neely at 650-723-5791.

This research study is looking for 120 boys with short stature in the United States. Stanford University expects to enroll 120 research study participants.

If you are 18 years or older, we are requesting that you read this consent form and sign it instead of your parent(s). You may still be in the treatment phase of study, but we may be following you to check your height, physical exam, lab testing and possibly imaging. This is a crucial component of the study to determine final height outcomes, to assess whether hormone production has returned to normal after treatment, and to reevaluate your bones.

DURATION OF STUDY INVOLVEMENT

We anticipate that treatment will last 2-3 years, depending on how far along your son is in puberty. We will follow your son until he reaches his final height, which could be 2-6 years after he starts the study.

PROCEDURES

Anastrozole (Arimidex) and letrozole (Femara) are once-a-day pills that have been used and studied extensively in trying to keep estrogen levels as low as possible in women with breast cancer. They also have been studied in boys in an effort to increase height. In boys, both medicines work well in reducing estrogen levels, possibly keeping the growth plates open longer, while allowing the boys to make testosterone and move through puberty. In the studies that have been done thus far, there has been an improvement in the predicted adult height in the boys using aromatase inhibitors. In addition, there have not been serious side effects noted in the studies done, but most have been short term in length.

If you choose to participate, Kirk Neely, MD and his research study staff will enroll you into the study. You will start taking the anastrozole pill daily. We will draw blood (about 2 teaspoonfuls) at the first visit and also obtain an XRAY of your son's wrist to assess the age of his bones. Enrollment in the study depends upon the initial hormone levels and XRAY results. We will be repeating the XRAY yearly. We will also arrange for a DEXA scan, which is like an XRAY, but in fact has less radiation

than a standard XRAY of the chest. The DEXA scan will help us determine your child's bone density, which is a theoretical concern since we are decreasing estrogen levels. We will be repeating this scan two years into the study to see if there has been any difference, and again at the end of the study. We will also perform a spine film at baseline and at two years.

We will see your son in our clinic every 6 months to obtain height measurements, assess how things are going with the medication, do a physical exam, and draw blood at those visits. Any samples left over after analysis will be destroyed when the study is completed.

We anticipate that your son will be on the medication for at least two years, but we will be following him until he stops growing which will be up to 6-7 years after we start the medication.

We have enrolled approximately 80 participants to date, a number likely sufficient for analysis. Until the results are adequately analyzed, we will use the less potent medication anastrozole exclusively. Boys starting anastrozole in this phase of study will still be seen every 6 months and then be followed annually after treatment until growth is completed. Laboratory and imaging studies will include blood tests and hand x-rays, which are necessary for clinical management. Data from this phase of the study will be collected for later analysis and potential publication.

PARTICIPANT RESPONSIBILITIES

As a participant, your responsibilities include:

- Follow the instructions of the Protocol Director and study staff.
- Take the study drug as instructed
- 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.
- Keep the study drug in a safe place, away from children and for your use only.
- 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 research study, you should not take part in any other research project without approval from the Protocol Directors of each study. 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.

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

To terminate participation simply inform your research doctor at your child's scheduled clinic visit or call Dr Kirk Neely at 650-723-5791 or contact him at neely@stanford.edu.

The protocol director may also withdraw you from the study and the study medications may be stopped without your consent for one or more of the following reasons:

- 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
- unanticipated circumstances

POSSIBLE RISKS, DISCOMFORTS, AND INCONVENIENCES

Possible risks, discomforts, and inconveniences of the study include pain, swelling and bruising that may occur at the site where blood is drawn. Monitoring for treatment adequacy through blood tests represents routine clinical care for patients during any hormone treatment. These discomforts are usually minor and temporary, and pain can be decreased when topical lidocaine based anesthetic cream is used. This cream is offered routinely to all children prior to blood tests but is usually not needed.

Other risks include the following:

- Arthralgia (sore joints)—not observed to date in boys.
- Changes in bone density. This has not been shown in short term studies but is a theoretical risk. This is the reason we will be doing DEXA scans at baseline and at two years into the study. A possible abnormality of the shape

of spine bones (vertebrae) was recently reported in boys after treatment, so we will also perform a spine film at baseline and at two years.

- Changes in testicular function. In animal model studies (rats and mice), there have been alterations in sperm function and in the size of the testes, but this has not been shown in boys using this medication.
- Higher than normal testosterone levels could cause hair loss or behavioral changes. Neither has been reported in studies to date.
- The expected reduction in estrogen levels, which results in the desired slowing of bone maturation, could also result in lower than expected growth factor levels and/or a slowing growth rate, which possibly could lead us to reduce the dose or stop the medication earlier than anticipated.

If your child participating in this study has a partner that is able to become pregnant, your child and his partner must use adequate contraception while he is participating in the study and for at least 12 weeks after taking his last dose of study medication. The doctor will discuss with your child what methods of birth control are considered adequate. You or your child should inform your study doctor if his partner becomes pregnant.

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

POTENTIAL BENEFITS

The benefits of the study include improved ultimate height for your child

WE CANNOT AND DO NOT GUARANTEE OR PROMISE THAT YOU WILL RECEIVE ANY BENEFITS FROM THIS STUDY.

ALTERNATIVES

The alternative to the study is not to participate.

PARTICIPANT'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 purpose of this research study is to obtain data or information on the safety and effectiveness of (insert name of drug, device, etc.); the results will be provided to the sponsor, the Food and Drug Administration and other federal and 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.

Authorization To Use Your Health Information For Research Purposes

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 are comparing the effects of two different aromatase inhibitors on growth and on different hormone levels. Your health information may be used in scientific publications but your identity will not be disclosed.

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 write to: Kirk Neely, MD at 300 Pasteur Drive, Rm G313, Stanford, CA 94305.

What Personal Information Will Be Used or Disclosed?

Your child's health information related to this study, including, but not limited to physical examination, hormone measurements and XRAY results 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 health information in connection with this research study:

- The Protocol Director: Kirk Neely, MD
- The Stanford University Administrative Panel on Human Subjects in Medical Research and any other unit of Stanford University as necessary
- Research Staff
- Pediatric Endocrinology Department

Who May Receive or Use the Information?

The parties listed in the preceding paragraph may disclose your 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
- Outside Laboratory for analysis: Esoterix specialty laboratory
- The Food and Drug Administration

Your information may be re-disclosed by the recipients described above, if they are not required by law to protect the privacy of the information.

When will my authorization expire?

Your authorization for the use and/or disclosure of your health information will expire on March 20, 2040.

Will access to my medical record be limited during the study?

To maintain the integrity of this research study, you may not have access to any health information developed as part of this study until it is completed. At that point, you would have access to such health

information if it was used to make a medical or billing decision about you (e.g., if included in your official medical record).

_____ _____
Signature of Adult Participant Date

_____
Print Name of Adult Participant

_____ _____
Signature of Legally Authorized Representative (LAR) Date
(e.g., parent, guardian or conservator)

_____
Print Name of LAR

_____
LAR's Authority to Act for Participant
(e.g., parent, guardian or conservator)

FINANCIAL CONSIDERATIONS

Payment
You will not be paid to participate in this research study.

Costs
If you participate in this study, there may be additional costs to you, including the cost of the medication, although it should be covered under most insurance policies. Additional costs also include the personal time it will take to come to all of the study visits. The study is not sponsored by a drug company and has no funding to cover the clinic visits, medication, laboratory studies, and imaging that are involved. Participation in this study is not a substitute for health insurance. You and/or your health insurance must pay for those services, supplies, procedures, and care that you require during this study for routine medical care. **You will be responsible for any co-payments and/or deductibles as required by your insurance.**

COMPENSATION for Research-Related Injury

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 Protocol Director and the research study staff will assist you in obtaining appropriate medical treatment. In the event that you have an injury or illness that is directly caused by your participation in this study, reimbursement for all related costs of care first will be sought from your insurer, managed care plan, or other benefits program. **You will be responsible for any associated co-payments or deductibles as required by your insurance.**

If costs of care related to such an injury are not covered by your insurer, managed care plan or other benefits program, you may be responsible for these costs. If you are unable to pay for such costs, the Protocol Director will assist you in applying for supplemental benefits and explain how to apply for patient financial assistance from the hospital.

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.

IRB USE ONLY
Approval Date: April 5, 2016
Expiration Date: April 5, 2017

CONTACT INFORMATION

Questions, Concerns, or Complaints: 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, Kirk Neely, MD. You may contact him now or later at 650-723-5791.

Injury Notification: If you feel you have been hurt by being a part of this study, please contact the Protocol Director, Kirk Neely, MD at 650-723-5791.

Independent Contact: 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, 3000 El Camino Real, Five Palo Alto Square, 4th Floor, Palo Alto, CA 94306.

Appointment Contact: If you need to change your appointment, please contact our scheduling department at 650-736-7642.

EXPERIMENTAL SUBJECT'S BILL OF RIGHTS

As a research participant you have the following rights. These rights include but are not limited to the participant'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 arise;
- 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.

May we contact you about future studies that may be of interest to you?

____ Yes ____ No

Signing your name means you agree to be in this study and that you will receive a copy of this signed and dated consent form.

_____ _____
Signature of Adult Participant Date

_____
Print Name of Adult Participant

_____ _____
Signature of Legally Authorized Representative (LAR) Date
(e.g., parent, guardian or conservator)

_____ _____
Print Name of LAR Authority to act for participant

_____ _____
(If available) Signature of Other Parent or Guardian Date

_____ _____
Print Name of Other Parent Authority to act for participant

The IRB determined that the permission of two parents is required for research to be conducted under 21 CFR 50.52, in accordance with 21 CFR 50.55 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

_____ _____

Signature of Person Obtaining Consent Date

_____

Print Name of Person Obtaining Consent