

STANFORD UNIVERSITY - Research Consent Form

Protocol Title: Insulin-like growth factor therapy

Protocol Director: Darrell Wilson, MD

IRB Approval Date: September 16, 2009

IRB Expiration Date: September 15, 2010

Human Subject's Bill of Rights: Persons who participate in a medical experiment are entitled to certain 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 to be reasonably expected; be given an explanation of any benefits to the subject to be reasonably expected, if applicable; be given a disclosure of any appropriate alternatives, drugs, or devices that might be advantageous to the subject and to be informed of their relative risks and benefits; be informed of the avenues of medical treatment, if any are available to the subject after the experiment, should complications 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the experiment or the procedures involved; be instructed that consent to participate in the medical experiment may be withdrawn at any time and the subject may discontinue participation without prejudice; be given a copy of the signed and dated consent form, and be given the opportunity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 or 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.

Are you participating in any other research studies? _____yes _____no

Insulin-like Growth Factor I Therapy

Purpose of the Study: You are invited to participate in a research study of insulin-like growth factor I (IGF-I). We hope to learn more about the safety and effective of IGF-1. Your child was selected as a possible participant in this study because you are going to start using IGF-1.

Introduction: Your child is to start treatment with insulin-like growth factor I (IGF-I). We have created this document for two purposes. First, we want you to be aware of the possible side effects of treatment. Although these side effects are uncommon, we feel you should be aware of them. Second, we sometimes review the records of our patients treated with various hormones and may publish these results. Any data that may be published in scientific journals will not reveal the identity of the patients.

IGF-I is a biosynthetic (made in a laboratory) form of the growth factor in the human body that is responsible for childhood growth. In the body, IGF-I is stimulated to act by growth hormone. Your child was probably treated with growth hormone for short stature, but it did not work as well as we anticipated. Therefore we have made the decision to treat him or her with IGF-I itself in hopes that IGF-I will be more effective than growth hormone has been.

IGF-I has been shown to be safe and effective in the treatment of patients who lack IGF-I of their own. It is approved by the Food and Drug Administration (FDA) for this use, and several hundred patients have been treated for IGF-I deficiency, also called growth hormone insensitivity. Some patients make intermediate levels of IGF-I or theoretically may make ineffective IGF-I of their own. Your child may be in this category and may benefit from IGF-I therapy, but the response is not as certain as in the children with definite IGF-I deficiency. We expect one or two patients per year to

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start IGF-I at Stanford.

Your child will receive IGF-I by twice daily injections. Your child will be observed at 3 to 6 month intervals. These visits will include a physical examination, height and weight measurements. At intervals, we may obtain x-rays, urine and blood tests. These tests will be obtained when clinically indicated.

Risks:

Hypoglycemia is uncommon but has been shown to occur after IGF-I injections. Hypoglycemia is a lowering of the blood sugar level. Some of the signs of hypoglycemia include: dizzy, tired, restless, hungry, unusual irritability, difficulty concentrating, sweating, tremor, nausea, and sensation of rapid or irregular heartbeats. If your child shows any signs of hypoglycemia, have your child drink some fruit juice to raise their blood sugar level and contact your child's study doctor if the symptoms don't go away or you have any questions. Your child's study doctor will tell you what to do if your child experiences any signs of hypoglycemia.

Lower than normal blood sugar levels have not been a problem when the IGF-I injections are followed by a meal. You should make sure that your child eats a meal within 15–30 minutes after each injection of study medication. You should not administer study medication if your child is ill and unable to eat. Check with your child's study doctor or nurse if this occurs.

In order to minimize the possibility that your child will have unusual lowering of blood sugar, the dose of IGF-I will be increased in steps, 40 micrograms per kilogram of weight for the first week and then to 80 micrograms per kilogram.

An event known as intracranial hypertension has been reported rarely in subjects treated with IGF-I. This condition results from increased pressure in the brain and can produce symptoms such as headaches, changes in vision, nausea, and vomiting. Symptoms usually occur within the first 4–6 weeks of treatment. Signs and symptoms should go away after stopping the medications.

There have been reports of increased size of tonsils, snoring, and ear problems in subjects treated with IGF-I. There have been reports of increased growth of soft tissue (nose, hands, feet) with IGF-I treatment.

There is a remote chance that your child will experience an allergic reaction to IGF-I. Allergic reactions may be mild, such as skin rash or hives, or severe, such as breathing difficulties or shock. A severe allergic reaction would require immediate medical treatment.

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Injection site pain, redness, and swelling have been observed in some subjects administered IGF-I. Injection site lipoatrophy (loss of fat) and lipohypertrophy (increase of fat) has also been observed. Injection site problems can usually be avoided by taking the injections in different parts of the body on different days.

Other adverse reactions that have been reported in some children treated with IGF-I include joint pain, muscle pain/tenderness, headache, sore throat, nausea, vomiting, rapid heart rate, seizures, abdominal pain, and back pain, swelling, fatigue, jaw pain and weakness. Most of these were probably not related to the treatment. Your child's condition will be monitored throughout the treatment and every precaution consistent with appropriate medical care will be taken.

IGF-I is known to cause cells to increase in number by dividing and multiplying. It is not known at this time whether IGF-I will promote tumor growth in humans. The relationship between IGF-I and these tumors is unknown at this time, and the possibility of causal relationships cannot be excluded, although the investigators in studies considered the tumors to be unrelated to IGF-I treatment in the majority of occurrences.

As is true with any drug, there may be unknown and potentially serious or life-threatening side effects that could occur with IGF-I.

During this study, your child's blood will be drawn for a variety of tests. The risks of drawing blood include temporary discomfort from the needle in your child's arm, possible bruising or swelling at the needle site, and, in rare instances, infection. If you request it, the nurse will provide you with a numbing cream called EMLA at the time your child is scheduled for blood tests.

There is a chance that IGF-I treatment could cause some of the other problems that have been rarely associated with growth hormone treatment:

- a disorder of the growth plate of the hip. This was not necessarily related to growth hormone treatment; however, any complaints of hip or knee pain should be promptly reported to your child's physician.
- development of antibodies (natural parts of a person's immune system). Very rarely children have developed sufficient immunity to growth hormone to make it ineffective.
- temporary diabetes mellitus.
- scoliosis (a curving of the spine. This worsening is also often seen during the normal pubertal growth spurt.
- a low thyroid state.

Although the potential risks listed above are rarely of clinical significance, your child's condition will be monitored throughout the study and every precaution consistent with the best medical care will be taken with regard to the IGF-I treatment. Although approved for some uses, growth hormone has not been approved by the FDA for all of the conditions we use it in.

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We may stop IGF-I therapy if we do not detect sufficient benefit or if significant side effects of the treatment are discovered. At the discretion of the protocol director, subjects may be taken out of this study due to unanticipated circumstances.

You understand that you may be withdrawn from the program without your consent (1) if you do not comply with the study instructions, (2) if you experience adverse reactions, (3) if the study is terminated, (4) for any reason thought appropriate by the study doctor, (5) for other administrative reasons, or (6) unanticipated circumstances.

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

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.

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

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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.

Your participation in this study is entirely voluntary. Your decision whether or not to participate will not prejudice you or your medical care. If you wish to participate in this study, you must sign this form. If you decide to participate, you are free to withdraw your consent, including your authorization regarding the use and disclosure of your health information and to discontinue participation at any time without prejudice to you or effect on your medical care. If you decide to terminate your participation in this study, you should notify Dr Wilson at 650 723-5791.

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

Your child is to start treatment with IGF-I. We have created this document for two purposes. First, we want you to be aware of the possible side effects of IGF-I treatment. Although these side effects are rare, we feel you should be aware of them. Second, we sometimes review the records of our patients treated with IGF-I and may publish these results. Any data that may be published in scientific journals will not reveal the identity of the patients.

Do I have to sign this authorization form?

You do not have to sign this authorization form. But if you do not, your child will not be able to participate in this research study or receive IGF-I. Signing the form is not a condition for receiving any medical care outside the study.

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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: Dr Wilson at 650 723 5791.

What Personal Information Will Be Used or Disclosed?

Your health information related to this study, may be used or disclosed in connection with this research study, including, but not limited to, your diagnosis, IGF-I dose, related records, physical examinations, x-rays, MRI's, and the like 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, Darrell Wilson, M.D.
- The Stanford University Administrative Panel on Human Subjects in Medical Research and any other unit of Stanford University as necessary
- Other members of the Division of Pediatric Endocrinology and Diabetes who might assist in your child's management or the conduct of this study.
- Other staff of the Stanford University Medical Center who might assist in your child's management or the conduct of this study.

Who May Receive / 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

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- The Food and Drug Administration.
- The Stanford University Administrative Panel on Human Subjects in Medical Research and any other unit of Stanford University as necessary.
- Other members of the Division of Pediatric Endocrinology and Diabetes who might assist in your child's management or the conduct of this study.
- Other staff of the Stanford University Medical Center who might assist in your child's management or the conduct of this study.
- The pharmaceutical company that makes IGF-I: Tercica.

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 December 31, 2036.

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 medical or billing decision about you (e.g., if included in your official medical record).

Signature of Legally Authorized Representative
(Parent, Guardian or Conservator)

Date

Signature of Legally Authorized Representative
(Parent, Guardian or Conservator)

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Cost

There is no cost to participate in this study. No payment will be provided for participation in this project. You or your insurance company will be responsible for some or all of the cost of therapy. The alternative to your participation in this study is your decision not to participate.

Withdrawal

Your child’s participation in this study is voluntary. You have the right to withdraw your consent for your child’s participation in this study at any time. If you do not choose to participate, or if you decide to withdraw, you may do so without any risk to your child’s further care at this institution.

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.
- Ask questions as you think of them.
- Tell the Protocol Director or research staff if you change your mind about staying in the study.

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. You may contact Dr. Wilson or his associates at (650) 723-5791.
- Emergency Contact: If you feel you have been hurt by being a part of this study, or need immediate assistance, please contact the Endocrinology Fellow at 650 497-8000, or the Faculty Sponsor, Dr. Wilson, at 650 723-5791.
- Alternate Contact: If you cannot reach the Protocol Director, please call our clinical nurse Eileen Durham at 650 723-6053.
- Independent of the Research Team Contact: If you are not satisfied with the manner in which this study is being conducted, or if you have any concerns, complaints, or general questions about the research or your rights as a research study subject, please contact the

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Stanford Institutional Review Board (IRB) to speak to an informed individual who is independent of the research team at (650)-723-5244 or toll free at 1-866-680-2906. Or write the Stanford IRB, Administrative Panels Office, Stanford University, Stanford, CA 94305-5401. In addition, please call the Stanford IRB at either (650)-723-5244 or toll free at 1-866-680-2906 if you wish to speak to someone other than the research team or if you cannot reach the research team.

Records relating to your child's participation in this study will be protected against release to unauthorized people. Members of the health care staff who care for your child have access to your child's file.

Any data that may be published in scientific journals will not reveal the identity of the subjects. Patient information will 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.

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 will 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 by signing this form.

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

Signature of Adult Patient

Date

Signature of Legally Authorized Representative
(Parent, Guardian or Conservator)

Date

Signature of Legally Authorized Representative
(Parent, Guardian or Conservator)

Date

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The IRB determined that the permission of one parent is sufficient for research to be conducted under 21 CFR 50.52, in accordance with 21 CFR 50.55.

I attest that the requirements for informed consent for the medical research project described in this form have been satisfied – that the participant has been provided with the Experimental Subject’s Bill of Rights, if appropriate, that I have discussed the research project with the participant and explained to him or her in nontechnical 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 participant to ask questions and that all questions asked were answered.

Signature of Person Obtaining Consent

Date

Print Name of Person Obtaining Consent

Participant ID:

