Please check one of the following:

_____ You are an adult subject in this study.

_____ You are the parent or guardian granting consent for a minor in this study.

Print minor's name here:
_________________________________________

The following information applies to the individual or to his/her minor child. If the subject is a minor, use of "you" refers to "your child."

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.

BACKGROUND

TrialNet is an international research group dedicated to the study, prevention, and early treatment of type 1 diabetes. Type 1 diabetes is an autoimmune disease. This means that the immune system (the part of the body that helps fight infections) mistakenly attacks and destroys the cells that produce insulin (islet cells found in your pancreas). The body’s ability to produce insulin decreases as the immune system destroys islet cells.

Oral insulin has already been tested in a diabetes prevention trial. In the overall study, oral insulin did not delay or prevent diabetes. However, the results suggest that oral insulin may delay diabetes in people with higher levels of insulin autoantibodies. This new study is being done to see if these findings are true in a similar group of people.
STANFORD UNIVERSITY Research Consent Form

Protocol Director: Darrell Wilson, MD

Protocol Title: Oral Insulin for Prevention of Diabetes in Relatives at Risk for Type 1 Diabetes Mellitus (Protocol TN-07)

This form describes the tests and procedures you will have if you are in the TrialNet Oral Insulin Diabetes Prevention Study. If you choose not to be in the Oral Insulin study, you can remain in the Natural History Study to be monitored for the possible development of type 1 diabetes.

PURPOSE OF RESEARCH

You have been participating in the TrialNet Natural History study. You are invited to participate in another TrialNet research study which is a diabetes prevention trial. The purpose of this study is to see if giving oral insulin will delay or prevent type 1 diabetes. You were selected as a possible subject in this study because you have had blood tests that show you have certain markers associated with an increased risk of developing type 1 diabetes. You have also had an Oral Glucose Tolerance Test (OGTT) that showed that your blood glucose levels are normal.

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 decide to participate, you are free to withdraw your consent, 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 Darrell Wilson, MD at 650-723-5791.

This international research study is looking for approximately 330 people with certain markers associated with an increased risk of developing type 1 diabetes. Stanford University expects to enroll ~50 research study subjects.

DURATION OF STUDY INVOLVEMENT

For this study, you will have an initial study visit, a three month follow-up visit, and then regular visits every six months while you are in the study.

The exact duration of the study is not known. We hope that the study will take no longer than 7-8 years from its start in 2007.

PROCEDURES

For this study, you will have an initial study visit, a three month follow-up visit, and then regular visits every six months while you are in the study.
At each study visit, we will also ask you questions about your family history and medical history. You will have a physical exam and blood tests. The total amount of blood collected for tests done at each study visit will be safe for your age and weight and for most people this will be about 4-7 tablespoons. These blood samples will be sent to central study laboratories for testing. As soon as the results are verified, these samples will be destroyed. Once a year, we will ask you questions about your activity and diet. You may refuse to answer any question you do not wish to answer. You can learn more about the study visits in the Research Volunteer Handbook.

Initial study visit
At the first study visit you will have a test called an Intravenous Glucose Tolerance Test (IVGTT). The IVGTT tells us how well the pancreas makes insulin. After an overnight fast (not eating during the night), glucose is given through a vein in your arm (intravenously). To make the blood sampling easier, we will place an intravenous needle and plastic tube (IV) in a vein in your arm. This IV will stay in your arm until the end of the test. Blood samples will be taken before you receive the glucose and then several times after the glucose is given. The entire test will take about 20 minutes. Females will also give a urine sample to be checked for pregnancy.

Most people will not need more than one IVGTT. However, in some cases we will ask for a second IVGTT to confirm the results of the first test. This can be done at the time of your next study visit.

As in the Natural History study, we will also test your blood to see if you have diabetes related autoantibodies. Autoantibodies are proteins that are made by the body's immune system. In diabetes, they are a sign that the cells in the pancreas that produce insulin could be damaged. These proteins can be found in the blood years before a person develops type 1 diabetes.

The results of your antibody and IVGTT tests will be used when we look at the results of the study to better understand the effects of oral insulin in different groups of people.

Randomization
Within seven weeks of having an OGTT, eligible participants will be divided into two groups by random assignment (similar to the flip of a coin). One group will then receive oral insulin. The other group will receive a placebo. (A placebo looks like medicine, but has no medicine in it). Neither you nor the researchers can choose what group you will be in. Neither you nor the researchers will know who is getting oral insulin and who is getting the placebo.
Follow-up visits
Your 3 month follow-up visit will consist of a brief medical history, a limited physical exam, blood testing, and pregnancy testing for female participants. You will be asked to come in for study visits every 6 months. We will ask questions about your health, do a physical exam, and perform a pregnancy test for female participants. We will also draw some blood for testing autoantibodies and HbA1c. An OGTT will be done in the morning after an overnight fast (not eating during the night). Your blood glucose (sugar) will be measured after you drink a sweet liquid that contains glucose over a 5-minute period. To make the blood sampling easier, we will place an intravenous needle and plastic tube (IV) in a vein in your arm. This IV will stay in your arm until the end of the test. Blood samples will be drawn through the IV before you drink the liquid and then at several times after you have finished drinking it. A total of about 1 tablespoon of blood will be drawn for the OGTT. The entire test will take about 2 hours. If any of the tests suggest that you have diabetes, you will be asked to confirm this result. This may require an additional OGTT. We will provide you with the study medication you will need to take until your next visit.

Phone calls
A research study team member will contact you every three months to ask about your health and to check that you are still taking your study medication.

Study Treatment
You will be asked to take a capsule every day. This should be swallowed as a capsule, if possible. If you cannot swallow capsules, you can mix the contents into juice or sprinkled onto a soft food (such as apple sauce).
Once the sample is taken, it will forever be separated or unlinked from your name. This will protect your identity and preserve anonymity. However, once you donate the sample, you will not be able to withdraw your tissues from the research project because the samples will not be traceable.

Disease testing and genetic research raises certain questions about informing you of any results. Possible risks of knowing results include: anxiety; other psychological distress; and the possibility of insurance and job discrimination. A possible risk of not knowing includes being unaware of the need for treatment. These risks can change depending on the results of the research and whether there is a treatment or cure for a particular disease. Sometimes patients have been required to furnish information from genetic testing for health insurance, life insurance, and/or a job. Donation of tissues for these research purposes is not genetic testing. (However, if you are interested in such clinical testing or genetic counseling, you should contact your physician.)

Even with special precautions, there is no absolute protection against discrimination on the basis of disease or genetic information. For this reason, the investigator will use the results of this study as research only and not include them in your medical record. Generally, you will not be told the results, even if there might be some potential benefit to you.

Any tissues you have donated which are used in research may result in new products, tests, or discoveries. In some instances, these may have potential commercial value and may be developed and owned by the Investigators, Stanford University and/or others. However, donors of tissues do not retain any property rights to the materials. Therefore, you would not share in any financial benefits from these products, tests, or discoveries.

As long as TrialNet continues, your stored blood samples could be used by TrialNet researchers and researchers from outside of TrialNet. However, if researchers from outside of TrialNet want to use your samples, they must first get permission from TrialNet researchers and the sponsor of this study, the National Institute of Diabetes & Digestive & Kidney Diseases (NIDDK).

When TrialNet is over, your blood samples will continue to be stored under the supervision of the NIDDK. Researchers would not be able to use your blood samples without the permission of the NIDDK.

**Stored Samples:**
With your permission, we will also draw up to an additional 3 tablespoons of blood for future studies. The amount of blood will be adjusted according to your body weight. Please indicate
whether you are willing to provide blood samples for storage. These blood samples could be used to help us learn more about what causes type 1 diabetes and about new ways of identifying people at risk for type 1 diabetes. They could also be used to help us learn more about type 1 diabetes, its complications (such as eye, nerve and kidney problems) and other conditions for which people with type 1 diabetes are at higher risk. Even if you decide not to have blood samples stored, you can still be in this study.

I give permission to have my blood stored: (check one below and initial)

- Yes, store all samples including the genetic samples _____ Initials
- Yes, store all samples but not the genetic samples _____ Initials
- No, I do not give permission to have any samples stored _____ Initials

SUBJECT’S RESPONSIBILITIES

You should:
- 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.
- Tell the Protocol Director or research staff if you believe you might be pregnant or gotten your partner pregnant.
- 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 all of the Protocol Directors. This is to protect you from possible injury arising from such things as extra blood drawing, extra x-rays, the possible interaction(s) of research drugs, or other similar hazards.
WITHDRAWAL FROM STUDY

Your choice to be in this study is completely voluntary. You may choose not to be in this study or to stop being in this study at any time. If so, you can continue your participation in the Natural History Study. Your current or future medical care will not be changed if you decide not to be in this study or to stop being in this study at any time.

The Protocol Director may also withdraw you from the study and the study medication may be stopped without your consent for one or more of the following reasons:

- Failure to follow the instructions of the Protocol Director and/or study staff.
- The Protocol Director decides that continuing your participation could be harmful to you.
- Pregnancy (if applicable).
- You need treatment not allowed in the study.
- The study is cancelled.
- Other administrative reasons.
- Unanticipated circumstances.

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.

There are some risks to having your blood drawn. These risks are discomfort and/or a bruise at the needle puncture site. Once in a while, some people may faint. It is rare, but some people may get an infection, form a small blood clot, get swelling of the vein and surrounding tissue or bleeding at the needle puncture site.

There are also some risks to the OGTT and IVGTT. Some people may feel nauseated when they have the OGTT. Some people may feel flushed when they have the IVGTT. There is the possibility that, instead of delaying or preventing the development of disease oral insulin could increase the destruction of islet cells in the pancreas. This would cause type 1 diabetes to develop more quickly.

WOMEN OF CHILDBEARING POTENTIAL

If you are a woman who is able to become pregnant, it is expected that you will use an effective method of birth control to prevent exposing a fetus to a potentially dangerous agent with unknown risk. If you are pregnant or currently breast feeding, you may not participate in
this study. You understand that if you are pregnant, if you become pregnant, or if you are breast-feeding during this study, you or your child may be exposed to an unknown risk.

To confirm to the extent medically possible that you are not pregnant, you agree to have a pregnancy test done before beginning this research study. You must agree to avoid sexual intercourse or use a birth control method judged to be effective by the investigator and which will not interfere with the proposed investigation. You must accept the risk that pregnancy could still result despite the responsible use of reliable method of birth control. You agree to notify the investigator as soon as possible of any failure of proper use of your birth control method, or if you become pregnant, either of which may result in your being withdrawn from the study.

**POTENTIAL BENEFITS**

No specific benefit can be promised you from your participation in this study. However, since you are at risk of developing diabetes, the close observation and frequent testing for diabetes may permit earlier detection and treatment of type 1 diabetes than would otherwise be the case. It is thought that early detection of type 1 diabetes and beginning of treatment may decrease both the immediate and long term effects of diabetes. The TrialNet research program might increase knowledge about the prevention of type 1 diabetes in the future. If you develop diabetes, it is possible that you could participate in another TrialNet study testing treatments to help preserve remaining insulin secretion at diagnosis.

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

**ALTERNATIVES**

Before you decide to take part in this study, we will talk with you about the other options available to you. You may choose not to participate in this study. At present, there is no established treatment for persons found to be at risk of developing type 1 diabetes. There may be other research studies that you can choose to be in.

**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 consent to be in this study includes consent for the TrialNet researchers to review all your health records as may be needed for the purposes of this study. Your consent gives TrialNet researchers permission to collect study information (data) related to this study and to use it for research purposes. Your consent also includes permission for the sponsor of this study and the Food and Drug Administration (FDA) and any other regulatory agencies, as may be required by law to review your study records and learn your identity if the study falls within their jurisdiction.

Information from your research records will be sent to our central coordinating center at the University of Southern Florida for statistical analysis. No personal information that directly identifies you will be included with this data. Personal information is information such as your name that directly identifies you. Instead you will be assigned a 3 letter abbreviation and a unique study code. The key to the code, linking your personal information to you, will be kept in a locked file here at Stanford University. Only Darrell Wilson, MD, and his study staff at Stanford University, will have access to the key to the code. The data obtained from this study will be combined with your Natural History data. After the study is completed, the study data may be placed in a government information bank and may become available to researchers under the supervision of the NIDDK/NIH. Your privacy will be protected whenever this information is used.

A Certificate of Confidentiality has been obtained from the National Institutes of Health (NIH). This is intended to further protect the confidentiality of information that we obtain about you. By having a Certificate of Confidentiality, TrialNet researchers are not required to give information that can be used to identify you. For example, we cannot be forced to give information about you to insurance companies. Also, we cannot be forced to give information about you for any civil, criminal, administrative, or legislative proceedings whether at the federal, state or local level. However, the Certificate of Confidentiality does not prevent you from giving this information to others, if you wish. Please understand that we will maintain the confidentiality of your research record, but we cannot guarantee the confidentiality of test results provided to you if you wish to share them with anyone.
There are some rare exceptions to the protection offered by the Certificate of Confidentiality. TrialNet researchers are not prevented from telling about matters such as child abuse, certain infectious diseases, or threatened violence to yourself or others.

TrialNet researchers will consider your records private. Rarely, representatives of the U.S. Department of Health and Human Services (DHHS) or TrialNet may review or ask for a copy of your study records. If this happens, we will provide your records. Also, employees of the Stanford University or its agents could be allowed to see your study records to make sure that the study is being done properly.

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. By signing this form you are agreeing to this. Your records and results will not be identified as belonging to you in any publication.

The purpose of this research study is to obtain data or information on the safety and effectiveness of Oral Insulin; the results will be provided to the sponsor, the Food and Drug Administration and other federal and regulatory agencies as required.
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?
The purpose of this study is to see if giving oral insulin will delay or prevent type 1 diabetes. Information from your research records will be sent to the central coordinating center at the University of Southern Florida for statistical analysis. After the study is completed, the study data may be placed in a government information bank and may become available to researchers under the supervision of the NIDDK/NIH.

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 Darrell Wilson, MD, 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, all information in a medical record, certain information indicating or relating to a particular medical condition, blood and other tissue samples and related records, physical examinations, x-rays, MRI's, etc.

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, MD
- The Stanford University Administrative Panel on Human Subjects in Medical Research and any other unit of Stanford University as necessary.
- Other members of the TrialNet Study team at Stanford University

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.
- The National Institutes of Health.
- The Food and Drug Administration, as well as other federal and state agencies as required by law.
- TrialNet Data Safety Monitoring Board.
• Other members of the TrialNet team at the other study sites and data collection centers.
• Blood specimens will be sent to central study laboratories for testing.

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, 2106.

**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 Subject      Date

_____________________________________ ______________
Signature of Legally Authorized Representative          Date

_______________________________________________
Description of Representative’s Authority to Act for Subject
STANFORD UNIVERSITY Research Consent Form

Protocol Director: Darrell Wilson, MD

 Protocol Title: Oral Insulin for Prevention of Diabetes in Relatives at Risk for Type 1 Diabetes Mellitus  (Protocol TN-07)

FINANCIAL CONSIDERATIONS

PAYMENT
You may receive up to $50 per in-clinic visit. Your travel expenses may also be covered (mileage, hotel and airfare, if necessary). Legally, you can be paid only if you are a US citizen, a legal resident alien (e.g., possess a "green") card), or have a work eligible visa sponsored by the paying institution.

COSTS
There is no cost to you for participating in this research study. There will be no charge for the visits, tests, or drugs required by the study.

SPONSOR
The National Institutes of Health is providing financial support and /or material for this study, with some financial support from the the Juvenile Diabetes Research Foundation (JDRF), and the American Diabetes Association (ADA).

The National Institutes of Health are providing some financial support for the facility and staff where part or all of the study is taking place.

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 him now or later, Darrell Wilson, MD, at (650) 723-5791. You should also contact him at any time if you feel you have been hurt by being a part of this study.

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

• Independent 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 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, 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 Trudy Esrey and/or Adriana Soto toll free at (877) 232-5182.

• Alternate Contact: If you cannot reach the Protocol Director, please page the research team at (650) 723-8222, pager # 1-8187. If you need immediate assistance please contact the page operator at (650) 497-8000 and ask for the “Pediatric Endocrinologist on Call”.

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 Protocol Director and the research study staff 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 TO PARTICIPATE BASED ON THE INFORMATION PROVIDED, AND THAT A COPY OF THIS FORM HAS BEEN GIVEN TO YOU.

_________________________________________          ________________
Signature of Adult Participant                 Date

_________________________________________          ________________
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 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

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