INFORMED CONSENT FORM –Non Diabetic

You are the parent or guardian granting permission for a child in this study.

Print child's name here: _____

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'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

We invite you and your child to take part in a research study about the differences in the brain development, memory and thinking of children with type 1 diabetes. The National Institutes of Health, which is a part of the federal government, is providing the funding for this study.

This study is being done to find out how diabetes impacts development of the brain, memory and thinking in young children. Your child is being asked to participate as part of a group that does not have diabetes as a comparison group (also called a "control" group).

There will be about 140 children with type 1 diabetes and about 70 children without diabetes in the study. The children will take part in the study at 5 centers in the United States. Your child will be in the study for about 18 months. At the beginning of the study, your child will have a Magnetic Resonance Imaging (MRI) of the brain at UCSF and complete a set of tests to measure intelligence and memory at Stanford.

You also will be asked to complete a brief set of similar tests and provide your education level and socioeconomic information. After 18 months, if there is funding available, we will ask you and your child to repeat this testing.

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, *a*nd 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 Bruce Buckingham 650-723-5791.

DURATION OF STUDY INVOLVEMENT

This research study is expected to take your child will be in the study for about 18 months.

	Enrollment/0	18m*
Eligibility assessment and consent	**X**	
Cognitive Testing	**X**	**X**
Brain MRI	**X**	**X**
Motor Skills Testing	**X**	**X**

Inclusion Criteria

To take part in the study, your child will need to:

(1) be at least 4 and not yet 8 years old

(2) have negative tests for markers of type 1 diabetes if a relative of someone with type 1 diabetes

- If your child has had these tests done in the last year, they will not be needed.
- If, however, your child has not had these tests in the past year, a sample of blood will be drawn from the vein in the arm to send to a laboratory for testing.
- If the results of your child's blood work are positive, the doctor will contact you to discuss the results.

(3) have been born term or near term (34 weeks or later without complications) and weighed more than 2kg (4.4 lbs) at birth

Exclusion Criteria

Your child cannot be in the study if he/she:

(1) has a history of mental retardation, language or learning disability or enrollment in a self-contained special education program

(2) has a known genetic or medical problem that could impair brain development

(3) has an abnormality of the brain/nervous system, visual or hearing problem

(4) has a history of abnormal blood sugar control

(5) has had previous inpatient psychiatric treatment

(6) has any contraindication to having an MRI of the head, including metal ear tubes, full set of braces in mouth (retainer is acceptable), other appliances, or vascular clip.

PROCEDURES

If your child enters the study, we will collect information about your medical history and your child's medical history. Your child will come to the clinic in the morning following an evening with no food or water (fasting). We will check your child's blood sugar. If your child's blood sugar is 110 mg/dL or higher, he or she will not be eligible to take part in the study. We will collect a blood sample for an HbA1c test. This test estimates a person's average blood sugar level for the 2-3 months before the test. We will do this test at the clinic and the result must be less than 6.0% for your child to continue in the study.

Thinking, Memory and Intelligence Tests

You will be asked to complete thinking and memory tests, some of which will be given on a computer. These tests will assess memory in real-life situations and general knowledge. For some of the tests, you will be asked to remember locations of dots on a computer screen, hit a button on the computer as fast as possible, mentally fit puzzle pieces together, and remember lists of words and locations of pictures on a page. You will also be asked to complete several school-like assessments, which include tests for vocabulary, fill-in-the-blank, math, puzzles and spelling. If you have diabetes, we will check your blood sugar to make sure it is between 70 and 300 mg/dL for the testing. If it is not, you may have to be rescheduled to complete the tests.

Your child will also be asked to complete similar thinking, memory and intelligence tests as described above.

Movement Test

Your child will be asked to complete a test that will assess his or her movements or what we call motor (or muscle) skills.

The testing that you will complete will take about 1 hour. The testing that your child will complete will take about 3 to 4 hours. You and your child will be allowed to take rest breaks during these tests. The results from you and your child's testing will be compiled and reviewed with you.

Magnetic Resonance Imaging (MRI) of the Brain

Your child will be scheduled for an MRI. The MRI scanner is a large tube that covers the body and uses strong magnets and magnetic waves to make images that show the structures in the brain. To prepare for the MRI, your child will be asked to view and listen to a short video of the scan place with the sounds that the machine makes. This helps make the children more comfortable during the study. We may also ask your child to practice lying in a mock scanner without magnets. This practice helps children feel more comfortable and makes it easier to do the real MRI scan. For the real scan, your child will be asked to lie still in the MRI scanner for about 30-60 minutes. During this time your child will not be exposed to x-rays, but rather a strong magnetic field and radiofrequency magnetic fields, which he/she will not feel. Your child will, however, hear repetitive tapping noises that arise from the Magnetic Resonance scanner. Your child may watch a DVD movie or listen to a CD or the radio during the scan. Your child may watch a DVD movie or listen to a CD or the radio during the scan. You or someone else

can sit beside your child during the scan to provide support, but you or the other person must be screened for metal implants or conditions that could be a hazard in the scan room.

If your child is not able to successfully complete the MRI scan, we may reschedule your child to come back to the clinic to try the MRI scan again. You may be asked to not let your child sleep as long as he or she normally would on the evening prior to the real scan. If your child is not able to complete the scan during the second attempt, your child will not continue in the study.

IF YOUR CHILD FEELS DISCOMFORT AT ANY TIME, NOTIFY THE OPERATOR AND YOU CAN DISCONTINUE THE EXAM AT ANY TIME.

A medical doctor (neuroradiologist) will review the MRI images. If the neuroradiologist thinks your child should receive additional medical follow-up based on the images, you will be notified. However, the type of MRI being done in this study is for research purposes and is not specifically designed to detect medical problems. It is possible there could be something in the images that the researchers would not notice. Do not rely on this research MRI to detect or screen for brain problems.

The scans performed in this study are for specific research purposes and are not optimized to find medical abnormalities. The investigators for this project may not be trained to perform medical diagnosis. The investigators and Stanford are not responsible for failure to find existing abnormalities with these MRI scans. However, on occasion the investigator may notice a finding on an MRI scan that seems abnormal. When this occurs, a physician will be consulted as to whether the findings merit further investigation, in which case the investigator will contact you and your child's primary care physician and inform you of the finding. The decision as to whether to proceed with further examination or treatment lies solely with you and your physician. The investigators, the consulting physician, and Stanford are not responsible for any examination or treatment that you undertake based on these findings. Because the images collected in this study may not comprise a proper clinical MRI scan, these images will not be made available for diagnostic purposes.

Testing at 18 Months
If there are funds available for the study, we will ask you and your child to return to the clinic to repeat the testing done at the beginning of the study.

PARTICIPANT RESPONSIBILITIES

As a participant, your responsibilities include

- Follow the instructions of the Protocol Director and study staff.
- 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.
- Complete your questionnaires as instructed.
- 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 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 and have your child participate is completely voluntary. You may choose not to be in this study or not have your child be in this study. You and your child can stop being in this study at any time. The study doctor may also choose to discontinue you and your child from study treatment at any time if it is felt that continuing treatment may hurt you or your child. This may happen if the side effects are too great, or if you do not follow the study instructions. You will be told of any new findings that affect you and your child being in this study.

The study may be changed or stopped at any time by the study group.

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

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

POSSIBLE RISKS, DISCOMFORTS, AND INCONVENIENCES

Taking part in research often involves some risks of physical or psychological injury or discomfort. Side effects will be different for each person. The most likely risks of this study are described below. You should discuss these with the study doctor. There is always the possibility that unknown or unexpected injuries might happen.

a. MRI Scan

Lying in the MRI scanner for 45-60 minutes may cause physical discomfort from trying to lie still. Some people get muscle aches and pains from lying on their back. We will try to make this easier this by providing cushions at pressure points and under the knees if needed. Earplugs or headphones will be used to reduce the sound of the MRI machine. Your child may watch a DVD or listen to music through the headphones to relax. Some people feel uncomfortable in a

confined place like the MRI machine. Your child will have a chance to get used to being in the MRI scanner before the MRI scan is done for the study. If your child feels too uncomfortable or afraid in the scanner, we may need to end the scan and reschedule this. If your child will have difficulty being still in the scan for as long as needed, we may ask you to not let your child sleep as long as he or she normally would the night before. While this may cause your child to be irritable before the scan, it may also help him or her sleep while in the scanner, allowing for a better chance of a successful scan.

There are no known risks of having an MRI for healthy people or those with diabetes. The MRI uses strong magnetic fields and weak radio waves. The strength of these and the length of the MRI for the study are similar to what would be done if someone needed an MRI outside of a study. Having an MRI is thought to be safe, and there are currently no limits on the number of MRIs that someone can have during their lifetime. Of course, there is the possibility that some unknown risk exists from having an MRI scan. If your child has any metal objects in the body, he or she will not be allowed to be in the study since this is a known risk.

b. Blood Drawing

Blood drawing can produce discomfort and/or a bruise. Once in a while, some people may faint. It is rare, but some people may get an infection, a small blood clot, swelling of the vein and surrounding tissue, or bleeding at the needle puncture site.

c. Thinking, Memory and Intelligence Tests

Taking the thinking, memory and intelligence tests may cause tiredness or boredom. You and your child will be allowed to take rest breaks during these tests. Some people may feel uncomfortable with researchers' having this kind of information about them or their child. It is possible that you will find the results of your child's testing upsetting.

POTENTIAL BENEFITS

The information from this study may increase the information available about how diabetes is related to memory and other thinking skills and the brain. Future patients with diabetes may benefit from what is learned.

It is possible that you and your child will not directly benefit from being a part of this study. A brief written summary of the thinking, memory and intelligence tests performed on your child will be shared with you. The brain imaging results regarding any changes in MRI of clinical importance also will be shared with you.

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

ALTERNATIVES

You can choose not to participate in 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.

CONFIDENTIALITY

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

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

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?
This study is being done to find out how diabetes impacts development of the brain, memory and thinking in young children. Your child is being asked to participate as part of a group that does not have diabetes as a comparison group (also called a "control" group). Results of the study will be reported in medical

journals and may be presented at scientific meetings. However, at no time will any of the participants in the study be identified. Confidentiality of you and your child's records will be maintained, and all records will be kept in accordance with current legal requirements.

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. 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 Bruce Buckingham 650-723-5791. Pediatric Endocrinology RM G313, MC 5208, Stanford, CA 94305-5208.

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, information that will be collected in this study. During your first visit, a blood sample may be collected to assess your child for markers for diabetes (this was discussed earlier). The blood sample will be sent to a laboratory to be tested along with the blood samples from all other patients in the study. The blood sample will only be identified by the code number assigned to your child for the study.

The MRI images taken at UCSF during the study will be sent to Stanford University, the Image Coordinating Center for the study, along with the images of all other participants in the study. The images will only be identified by the code number assigned to your child for the study.

The results of the thinking, memory and intelligence tests will be provided to the researchers at Washington University in St. Louis who will be scoring the tests of all participants in the study. The test results will only be identified by the code number assigned to your child for the study.

The results of your examinations and testing will be collected in a central computer at the Jaeb Center for Health Research (the DirecNet study coordinating center) in Tampa, Florida along with information from all other patients in the study. This information will be identified only by a code number assigned to you and your child. A signed copy of this consent form will be sent to the Jaeb Center for Health Research. The forms will be kept in a secure file cabinet separate from the data collected for the 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 Bruce Buckingham
- The Stanford University Administrative Panel on Human Subjects in Medical Research and any other unit of Stanford University as necessary
- Research Staff

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
- JAEB center for Health Research
- National Institutes of Health
- Food and Drug Administration
- The data safety monitoring board
- Other centers participating in the study

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.

Reviewers of your and your child's health information may include representatives of the Jaeb Center, the researchers in DirecNet, the laboratory that will measure the blood samples, any review board that oversees human investigations regulations for your doctor's office or institution, the Food and Drug Administration (FDA) or any federal agency that oversees the conduct of clinical trials. If your research record is reviewed by any of these groups, they may also need to review your entire medical record.

When will my authorization expire?

Your authorization for the use and/or disclosure of your health information will expire December 31, 2050.

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 Legally Authorized Representative Date

_____

Description of Representative's Authority to Act for Subject

FINANCIAL CONSIDERATIONS

Payment

You will be paid $100 cover travel and other expenses related to the testing that is done at the start of the study. If your child attempts the MRI but is not successful and a second attempt is needed, an additional $50 will be paid for the second attempt (up to a maximum of $150 for the baseline testing). If the study has funding to repeat testing at the 18-month visit, you will be paid an additional $100 for completion of the MRI and testing at 18 months (up to a maximum of a $150 if the first attempt is unsuccessful and a second attempt is made to complete the 18-month testing). Additional travel expenses may be paid in select cases for subjects with higher expenses based on need.

You may also be given a small token of appreciation valued under $20 at study visits

Payments may only be made to U.S. citizens, legal resident aliens, and those who have a work eligible visa.

Costs

The study will be paying for the costs of the research procedures that are part of the study, including the MRI, special memory and intelligence tests.

If you participate in this study, there may be additional costs to you. These include the personal time it will take to come to all of the study visits.

The study will pay for those services, supplies, procedures, and care associated with this study that are not a part of your routine medical care. If you would like to review the list of such covered services, supplies, procedures and care, please tell us now or at any time during the study.

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.**

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

Dr. Bruce Buckingham is a paid consultant to Medtronic MiniMed, and has received payment for lectures from Medtronic MiniMed and Abbott, companies which are providing devices used in this study. Ms. Block has received payment for a paper and for talks from Abbott, and for talks from Medtronic MiniMed.

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.

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, Bruce Buckingham. 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, Bruce Buckingham 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, MC 5579, Palo Alto, CA 94304.

Appointment Contact: If you need to change your appointment, please contact Kimberly Caswell at 650-724-1201, kcaswell@stanford.edu

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.

Please indicate whether you are willing to participate and whether you are willing to have your child participate in this study (select one):

☐ *I agree to participate and have my child participate in this study* _____ *Initials*

☐ *I do not agree to participate in this study as a study subject myself, but do give permission for my child to participate in this study* _____ *Initials*

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 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 50.51, 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