Consent and Authorization Document

Informed Consent and Authorization Document

Study Title: The Use of Low-Dose Carvedilol to Improve Hypoglycemia Awareness in Patients with T1DM

Protocol No.: IRB_00108879

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INTRODUCTION

You are being asked to take part in a research study. Before you decide, it is important for you to understand why the research is being done and what it will involve. Please take time to read the following information carefully and discuss it with friends and relatives if you wish. Ask the research doctor or staff if there is anything that is not clear or if you would like more information. Take time to decide whether or not to volunteer to take part in this research study.

BACKGROUND

Many individuals with Type 1 diabetes lose the ability to recognize when their blood sugars start to fall – something we call "hypoglycemia unawareness". This can be problematic because not being able to recognize when blood sugars fall means that the patient cannot take the necessary corrective actions to help raise their blood sugars back to normal levels, for example, by drinking juice, eating or taking a sugar tablet. To date, we do not fully understand why this happens and there is currently no drug treatment that is available to improve awareness of falling blood sugars other than to try to avoid low blood sugar attacks for several weeks. The brain plays an important role in sensing falling blood sugar levels and then tells the body to release the necessary hormones that 1) help counter this fall and 2) trigger the symptoms that make us aware our blood sugars are falling. The brains of patients with Type 1 diabetes, especially those who have recently experienced an episode of low blood sugar, lose the ability to sense the fall in blood sugar levels and hence they are not able to recognize or recover from these low blood sugar attacks. Research in this field has shown that when blood sugars fall, the brain releases a chemical called noradrenaline which triggers awareness of low blood sugars. However, repeated stimulation of this system (such as when one experiences multiple low blood sugar attacks) does the opposite and can actually impair one's ability to sense "lows". So, the purpose of the study is to evaluate whether the drug carvedilol which is from a class of drugs called beta-blockers, can be used safely to block some of the actions of noradrenaline to help restore awareness of falling blood sugars. Carvedilol is an FDA-approved drug for managing blood pressure and studies have shown that this drug may be useful for treating

hypoglycemia unawareness. This study is sponsored by the Juvenile Diabetes Research Foundation (JDRF) and is being conducted by Drs. Owen Chan, PhD, Matthew Wahl, MD and Simon J. Fisher, MD, PhD here at the University of Utah. This is a Phase 2 study which means it is being done on a larger number of human subjects to find out if the drug works and does what it is supposed to do. Participation in this study will last up to 5 weeks.

STUDY PROCEDURES

Informed Consent: Prior to conducting any study-related procedures, we will obtain written informed consent from you as the participant. The nature, scope and possible consequences, including risks and benefits, of the study will be explained to you by the principal investigator (PI) or his designee in accordance with the regulations and guidelines in the Statement of Compliance. You will then be given the opportunity to review and ask questions related to the information in the consent form and about the study before signing. Please note that *your decision to participate or not to participate in this study will in no way influence your current or future standard of medical care*.

Screening Procedures: At screening, we will assess for your eligibility to take part in the study against a set of conditions. Individuals who do not meet the conditions for entry into the study will not be allowed to participate in the study. The reason(s) for ineligibility will be documented in your research chart. After enrollment, we will collect some information about you including: **Demographics and Medical History:** This is information about your gender, age, date of birth, race, ethnicity, diagnosis of (condition), and other relevant past medical history will be collected and recorded in your research file. **Laboratory Variables:** In addition, we will draw blood samples from you for routine laboratory tests. In the case of females, we will ask that you take a pregnancy test. **Physical Examination:** A complete physical examination will be conducted to check your lungs, heart, abdomen as well as your nerve function. **Vital Signs:** Vital signs, including measurement of your blood pressure, heart rate, breathing rate and O_2 saturation. **Electrocardiogram (ECG):** An ECG will be completed during the screening period to look for abnormalities in your heart. **Continuous Glucose Monitor (CGM):** A blinded continuous glucose monitor (CGM) will be placed on you after enrollment and you will be asked to continue to wear this device until the end of the study. A "blinded" device means you will not be able to see the blood sugar reading on the device but it will continue to record your blood sugars and we can download this data when you come into the office. During this time, we ask that you change the sensors on a regular basis (every 6 days) or you can come into the office and have one of our research staff change it for you. **Glucometer:** You will also be provided with a Bayer Contour Next EZ® glucometer to use during the study to check your blood glucose levels and to calibrate the CGM. We will show you how to use it. **Hypoglycemia Log:** During the study, we also ask that you write down in a book (the book will be given to you) whenever you feel your blood sugar is low and also check your blood sugar with a finger stick and the provided glucometer and record it in the book as well. We ask that you try to avoid hypoglycemia for the 24hours prior to admission to the hospital for the study.

Overnight Hospital Stay: About six (6) days after you are started on the CGM, you will be asked to reduce the dose of long-acting insulin (if applicable) prior to coming to the hospital. This to help reduce your chances of have a low blood sugar attack when you fast overnight. The night before the clamp study, you will be admitted into the hospital and the CGMs will be checked for a low blood sugar reading (a reading

of less than 75mg/dl. If a reading of less than 75mg/dL is noted within 24 hours of beginning the "clamp" study, then the study will be delayed for one week. In addition, female participants will be asked to take a pregnancy test to ensure they are not pregnant. If you qualify to go on in the study, we will provide you with a meal before asking you to fast overnight. The hospital nursing staff will insert an intravenous insulin drip into your arm and your blood sugar levels will be maintained at normal levels (between 90-120mg/dl) during the overnight fasting period. The nurses will check your blood sugars with a finger prick periodically throughout the night.

First Glucose Clamp*:* The next day, you will take part in a "glucose clamp" study. This procedure is call a "glucose clamp" because we use insulin and glucose to adjust and hold (i.e. "clamp") your blood sugar (i.e. "glucose") at a set level. A second catheter will be inserted into the hand vein of the arm opposite to your insulin drip line for blood sampling and that hand will be placed into a heated (~55°C) box. You will be lying down in bed for the entire procedure. An ECG will also be connected to you to monitor heart activity. Heart rate, blood pressure and ECG will be monitored every 15 minutes throughout the study. We will draw a blood sample (30mL) from you before we start the study. In addition, we will ask you to fill in a short questionnaire about your perception of hypoglycemia symptoms. Subsequently, you will be given a potassium chloride tablet to help maintain your potassium levels during the experimental procedure. Once these steps have been completed, we will infuse a combination of insulin and glucose through your IV line and gradually lower your blood glucose levels in stages, checking blood glucose levels every 5 minutes from a 1ml blood draw. At each stage, we will draw blood samples and ask you to fill in a questionnaire. Your blood sugar levels will go no lower than 45mg/dl and no more than five 30mL blood draws will occur during the study. At the end of the study, we will gradually bring your blood sugar levels back up to normal and provide you with a meal to aid recovery. Once the procedure has been completed and the nursing staff feels you are stable enough to be released from the hospital, we will provide you with some glucose tablets, your drug treatment medication, instructions on how to take the medication and information on whom to contact in case of medical concerns. You will not be allowed to drive after the procedure and will need someone to drive you home. By consenting to participate in this study, you agree to not drive a vehicle following the glucose clamp procedure and will arrange for a ride home.

Drug Treatment. At the end of the first experimental procedure, you will be supplied with either placebo or one of two different doses of carvedilol. A placebo is a "dummy pill" which looks exactly like the pill containing the study drug but it contains no drug or active ingredients. Study participants are given placebos so that the effects of a drug can be compared against no drug. Use of placebos prevents the participant and the doctor from knowing whether or not the subject is getting the drug. Neither you nor the research team will know which treatment you are receiving. This is what we call a "double-blinded" trial. Your treatment will be kept in sealed records and in the event of an emergency, the research staff can find out which treatment you received. This is a "randomized trial" which means that a computer decides by chance which treatment you will receive, not the doctors running the trial. Your chances of getting the study drug are 67%.

Follow-Up Visit: About 7 days after the start of the intervention phase, we ask that you come into the clinic for a follow-up visit where vital signs, side effects and CGM data will be monitored or evaluated.

Second Glucose Clamp*:* At the end of four weeks of drug or placebo treatment, you will be asked to return to the hospital for an overnight stay and a second hypoglycemic clamp procedure. The second hypoglycemic clamp procedure will be identical to the first one described above.

RISKS

Continuous Glucose Monitoring (CGM): CGM is commonly used in patients with diabetes and is considered to be diagnostic and therapeutic in patients that frequently experience low blood sugars or who do not recognize their "lows". Minor pain may be experienced during the sensor insertion. Skin irritation at the sensor insertion site has been reported. Infection is possible if the site cleaning is not done before sensor insertion. Damage to the sensor may cause electrical shocks.

Blood Sampling: Blood draws or fingersticks with a lancet will be conducted as described above. Localized pain, bleeding, bruising, infection, dizziness and faintness can occur during blood sampling.

Glucose Clamp: The major risk associated with these studies stem from the clamp procedures. Insertion of intravenous catheters brings the risk of infection, swelling or bruising at the site of insertion. Localized pain, bleeding, bruising, infection, dizziness and faintness can occur during blood sampling. During the clamp, low blood glucose may trigger typical symptoms of hypoglycemia which include tremors, sweating, palpitations, increased heart rate, confusion, drowsiness, speech difficulty, nausea, headache and impaired vision. In addition, the provision of fluids during the procedure may increase urinary urgency in participants.

Adverse Effects of Carvedilol:
The Food and Drug Administration (FDA) reported adverse effects of carvedilol include the following:

Body as a Whole: allergy, malaise, hypovolemia, fever, leg edema.
Cardiovascular: fluid overload, postural hypotension, aggravated angina pectoris, AV block, palpitation, hypertension.
Central and Peripheral Nervous System: hypoesthesia, vertigo, paresthesia.
Gastrointestinal: melena, periodontitis.
Liver and Biliary System: SGPT increased, SGOT increased.
Metabolic and Nutritional: hyperuricemia, hypoglycemia, hyponatremia, increased alkaline phosphatase, glycosuria, hypervolemia, diabetes mellitus, GGT increased, weight loss, hyperkalemia, creatinine increased.
Musculoskeletal: muscle cramps.
Platelet, Bleeding and Clotting: prothrombin decreased, purpura, thrombocytopenia.
Psychiatric: somnolence.

Reproductive, male: impotence.

Special Senses: blurred vision.

Urinary System: renal insufficiency, albuminuria, hematuria.

REPRODUCTIVE RISKS

It is possible that if the treatment is given to a pregnant woman it will harm the unborn child. Pregnant women must not take part in this study, nor should women who plan to become pregnant during the study. Women with childbearing potential will be asked to have a pregnancy test before taking part to exclude the possibility of pregnancy. If you can become pregnant, you must use an effective contraceptive during the course of this study. Acceptable methods of birth control include hormonal contraceptives (oral, patch or injection), intrauterine device, dedicated and correct condom use, birth control ring or diaphragm and female or male (partner) sterilization. If you become pregnant while taking part in the study, you must immediately tell your research doctor. Options will be discussed with you at that time. Whether or not you remain on study treatment, we will follow the outcome of your pregnancy and we will continue to follow you according to the study plan.

UNFORESEEABLE RISKS

In addition to the risks listed above, participation in this study may involve risks that are currently unforeseeable and you may experience a previously unknown risk or side effect.

BENEFITS

While we cannot promise any direct benefits to you from your taking part in the study, the information we get from this study may help us better treat patients with diabetes in the future. If the treatment is effective, you may see an improvement in your ability to sense a low blood glucose event.

ALTERNATIVE PROCEDURES

You may choose not to be in this study. If you do not want to take part in the study, you will still continue to receive the same medical care from your care provider(s). Your decision will not affect your relationship with your doctor or the study team in any way.

PERSON TO CONTACT

If you have questions, complaints or concerns about this study, you can contact either Dr. Owen Chan, Ph.D. at 801-585-0444 or Drs. Matthews Wahl, M.D. or Simon J. Fisher, M.D., Ph.D. at 801-581-7761. If you think you may have been injured from being in this study, please call either Dr. Chan or Dr. Lin at the numbers listed above. For any urgent needs or concerns about the study or study drug, please call the University of Utah Hospital Operator at 801-581-2121 where an on-call Endocrinologist can be reached 24-hours a day.

Institutional Review Board: Contact the Institutional Review Board (IRB) if you have questions regarding your rights as a research participant. Also, contact the IRB if you have questions, complaints or concerns which you do not feel you can discuss with the investigator. The University of Utah IRB may be reached by phone at (801) 581-3655 or by e-mail at irb@hsc.utah.edu.

Research Participant Advocate: You may also contact the Research Participant Advocate (RPA) by phone at (801) 581-3803 or by email at participant.advocate@hsc.utah.edu.

RESEARCH-RELATED INJURY

If you are injured from being in this study, medical care is available to you at the University of Utah, as it is to all sick or injured people. The University of Utah has not set aside any money to pay the costs for such care. The University will work with you to address costs from injuries. Costs would be charged to you or your insurance company (if you have insurance), to the study sponsor or other third party (if applicable), to the extent those parties are responsible for paying for medical care you receive. Since this is a research study, some health insurance plans may not pay for the costs. By signing this consent form you are not giving up your right to pursue legal action against any parties involved with this research.

The University of Utah is a part of the government. If you are injured in this study, and want to sue the University or the doctors, nurses, students, or other people who work for the University, special laws may apply. The Governmental Immunity Act of Utah is a law that controls when a person needs to bring a claim against the government, and limits the amount of money a person may recover. See sections 63G -7-101 to -904 of the Utah Code.

VOLUNTARY PARTICIPATION

Research studies include only people who choose to take part. You can tell us that you don't want to be in this study. You can start the study and then choose to stop the study later. We will still give you medical care and answer any questions you have. Your decision will not affect your relationship with your doctor or the study team in any way. Your decision will in no way influence the current or future standard of medical care that you are receiving.

If you want to stop being in this study, please let the research doctor know. That way you can find out what should be done about your normal medical care outside of the study.

RIGHT OF INVESTIGATOR TO WITHDRAW PARTICIPANTS

The research doctors can withdraw you without your approval. Possible reasons for withdrawal include the development of severe hypoglycemia or other severe adverse event requiring an emergency room visit or hospitalization, the inability/poor adherence in completing the study protocol such as fingerstick monitoring, failure to use provided glucometer, treatment intake and hypoglycemia log or CGM maintenance. If a participant withdrawal is considered, a review of the case will be conducted with all the major research doctors, and the decision will be informed to you. You will be asked to return the unfinished pills, the hypoglycemia log and CGM device. The research data may still be used for study analysis, future study design and publication. Your compensation may not be provided to you if the withdrawal is due to a lack of adherence to the study protocol. If the withdrawal is due to an adverse event, for your health and welfare, a follow-up may be requested.

COSTS AND COMPENSATION TO PARTICIPANTS

The study drug and study-specific procedures listed in the "Study Procedures" section of this consent will be supplied to you at no cost. You will not be charged, nor will your insurance company be charged, for

any test, procedure or visit that is completed solely for the purpose of this study. You will still be responsible for the cost of your usual ongoing medical care, including procedures and/or non-study medications that your regular doctor requires during this study as part of your usual medical care. If you have any questions, please ask the study doctor or a member of the study team.

Depending on the distance you travel to the study site and lost work or personal time, you will be offered reimbursement to help offset your travel time, lost work and personal time. You will only be reimbursed for those visits that you complete. Please tell the study staff if you are in need of travel and loss work reimbursement. If you would like to be reimbursed it is necessary for the University of Utah to collect your Social Security Number. You will provide this information for a Federal W-9 Form that is filed with our Accounts Payable Department at the University of Utah. The amount you receive for travel and time reimbursement will be turned into the Internal Revenue Service (IRS) as taxable income. You can choose not to provide us with your Social Security Number for this form and still participate in this study; however, we will not be able to pay you as outlined in this consent form. It may take a few weeks for the paperwork to be processed and then you will receive a check from the University of Utah. If you have any questions, please ask the study doctor or study staff.

You will be reimbursed for each study visit that you complete. This amount is meant to cover your expenses including travel and loss of work time. This compensation is not meant as a gift or incentive to take part in this research study. Reimbursement will be dispersed as follows:

Visit 1: $20
Visit 2: $30
Visit 3: $400
Visit 4: $50
Visit 5: $800

NEW INFORMATION
Sometimes during the course of a research project, new information becomes available about the investigational drug or treatment that is being studied. If this happens, your research doctor will tell you about it and discuss with you whether you want to continue in the study. If you decide to withdraw at that time, your research doctor will make arrangements for your medical care to continue. If you decide to continue in the study, you may be asked to sign an updated consent form. Also, on receiving new information your research doctor might consider it to be in your best interests to withdraw you from the study. He/she will explain the reasons and arrange for your medical care to continue.

NUMBER OF PARTICIPANTS
We expect to enroll 21 participants at the University of Utah for this study.

AUTHORIZATION FOR USE OF YOUR PROTECTED HEALTH INFORMATION
Signing this document means you allow us, the researchers in this study, and others working with us to use some information about your health for this research study.

This is the information we will use and include in our research records:

- Demographic and identifying information like name, address telephone number and email address.
- Social Security Number – you have the option to withhold your social security number and still participate in the study.
- Related medical information about you like medical and social history, family medical history, allergies, current and past medications or therapies, and information from physical examinations, such as blood pressure reading, heart rate, temperature and lab results. This information is only available as part of your medical chart and *will not* be collected as study data or disclosed outside of the hospital.
- Record pertaining to your study visits.
- All study procedure results as listed in the Study Procedures section

Personal data (including your medical findings) that are important to this study will be coded and transferred to separate study documentation sheets and/or stored electronically.

If you do not return for study visit(s) or are considered lost to follow up the study doctor will try to contact you with at least one telephone call and one written message. If these attempts to contact you directly are not successful, the study doctor will try to get information about your well-being from other sources in compliance with local regulations.

How we will protect and share your information:

- We will do everything we can to keep your information private, but we cannot guarantee this. Study information will be kept in a secured manner and electronic records will be password protected. Study information may be stored with other information in your medical record. Other doctors, nurses, and third parties (like insurance companies) may be able to see this information as part of the regular treatment, payment, and health care operations of the hospital. We may also need to disclose information if required by law.

- A description of this clinical trial will be available on http://www.ClinicalTrials.gov, as required by U.S. Law. This website will not include information that can identify you. At most, the website will include a summary of the results. You can search this website at any time.

- In order to conduct this study and make sure it is conducted as described in this form, the research records may be used and reviewed by others who are working with us on this research:
    - Members of the research team;
    - The University of Utah Institutional Review Board (IRB), which reviews research involving people to make sure the study protects your rights;
    - The study sponsor: Juvenile Diabetes Research Foundation
    - A study research coordinator;
    - University of Utah Department of Population Health Sciences, which will conduct the statistical analyses;

- Potential sponsors for future investigations, including, but not limited to: National Institute of Health, American Diabetes Association, Juvenile Diabetes Research Foundation;
- Medical journals or meetings, that will publicize the research data and the new medical knowledge to the medical field.

- If we share your identifying information with groups outside of *the* University of Utah (e.g., the Food and Drug Administration), they may not be required to follow the same federal privacy laws that we follow. They may also share your information again with others not described in this form.

- If you do not want us to use information about your health, you should not be part of this research. If you choose not to participate, you can still receive health care services at the University of Utah.

What if I decide to not participate after I sign the Consent and Authorization form?

You can tell us anytime that you do not want to be in this study and do not want us to use your health information. You can also tell us in writing. If you change your mind, we will not be able to collect new information about you and you will be withdrawn from the research study. However, we can continue to use information we have already started to use in our research, as needed to maintain the integrity of the research.

This authorization does not have an expiration date.

You have a right to information used to make decisions about your health care. However, your information from this study will not be available during the study; it will be available after the study is finished.

CONSENT

I confirm that I have read this consent and authorization document and have had the opportunity to ask questions. I will be given a signed copy of the consent and authorization form to keep.

I agree to take part in this research study and authorize you to use and disclose health information about me for this study, as you have explained in this document.

_____
Participant's Name

_____ _____
Participant's Signature Date

_____
Name of Person Obtaining Authorization and Consent

_____ _____
Signature of Person Obtaining Authorization and Consent Date

_____