IRB NUMBER: 2012-665
IRB APPROVAL DATE: 03/08/2018
IRB EXPIRATION DATE: 09/05/2018

ALBERT EINSTEIN COLLEGE OF MEDICINE OF YESHIVA UNIVERSITY
MONTEFIORE MEDICAL CENTER

You are being asked to join this research study.
The title of the study is: **Mechanisms of Hypoglycemia Associated Autonomic Failure**
The study is being done under the supervision of: **Dr. Meredith A. Hawkins,M.D**. Principal Investigator (Researcher Study Doctor): **Dr. Meredith A. Hawkins** Office Address: **1300 Morris Park Avenue, Bronx, NY 10461**
Telephone #: **(718) 430-3186**

Protocol #: **2012-665**

DO I HAVE TO TAKE PART IN THIS RESEARCH STUDY?

• Your participation is voluntary. This means that you decide whether or not you want to join the study after speaking with the researcher, or other member of the research team.
• If you decide to take part you will be asked to sign this consent form. Your signature means that you agree to be a subject in this research.
• After reading this form and having a discussion about what it says, you should ask all the questions you want to ask. You should take as much time as you need to make a decision.
• If you do not understand some of the terms used in this form, ask the person who is discussing the study with you to give any additional information that may make this easier to understand.
• You do not have to consent to participate in the study immediately, or ever. Take time to decide whether or not you wish to join. You may take home a copy of this consent form to think about it or discuss the information with family or friends before you decide.
• If you decide not to participate the care providers at this facility will give you all of the standard care that is appropriate for you.
• You will be given a copy of this form whether or not you agree to participate in this study. Do not sign the form unless you have had all your questions answered and understand exactly what is involved.
• If you decide to take part you are still free to withdraw at any time without giving a reason. This will not affect your care and you will continue to be treated at this facility.
• If you decide to withdraw after receiving the study drug, you should talk with the research study doctor to see how best to complete the withdrawal process.
• The form discusses:
WHAT THE RESEARCHERS WILL LEARN FROM THE RESEARCH
WHAT WILL HAPPEN TO YOU DURING THE RESEARCH
WHAT RISKS AND/OR DISCOMFORTS YOU MIGHT EXPECT/EXPERIENCE AS A RESEARCH SUBJECT
IF YOU CAN EXPECT ANY BENEFITS, AND ARE THERE ANY ALTERNATIVES TO THIS RESEARCH FOR YOUR CONDITION.

TYPE 1 DM

STUDY SPECIFICS

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• One of the main barriers to appropriate insulin treatment in patients with diabetes is the fear from low sugar (glucose). Taking too much insulin, insufficient meals, or doing exercise – all can result in low blood glucose. Having low glucose can be a devastating complication and patients with diabetes sometimes try to avoid it by taking less insulin, eating more or avoiding exercise. The purpose of this study is to understand how and why the body reacts to low glucose, and to find ways to improve the treatment for diabetes.

WHY HAVE I BEEN ASKED TO TAKE PART IN THIS RESEARCH STUDY?

• You are being asked to participate in this study because you suffer from type 1 diabetes. Patients with type 1 diabetes are the most vulnerable to low blood glucose and could benefit from improvement in their body responses to low blood glucose.

WHY IS THIS RESEARCH STUDY BEING DONE?

• This research is being done to better understand how the body reacts to low sugar, how and why this reaction is different in patients with type 1 diabetes, and what methods we can use to improve the response to low glucose.
• Improving the responses to low glucose can have an enormous impact on how patients with type 1 diabetes are being treated, on their quality of life and possibly on their diabetic complications.

HOW MANY PEOPLE WILL TAKE PART IN THE RESEARCH STUDY?

• This research represents the first phase of a larger study, and for this phase 24 subjects will be enrolled (range in age from 18 to 55 years): 12 subjects with type 1 diabetes mellitus and 12 healthy non-diabetic subjects.

WHAT WILL HAPPEN IF I TAKE PART IN THIS RESEARCH STUDY?

• Before you can be admitted to this study, you must receive medical testing (screening tests) at the Clinical Research Center (CRC) to determine whether you are eligible to participate. The testing will include a physical examination, routine blood tests, urine toxicology screen, a routine urine test and an EKG.
• Your participation may involve four studies, which will be at least 6 weeks apart. Each study will last two days. There will be no specific order in choosing to perform one study or another.
• Subjects using narcotic drugs, pain killers or drugs used for insomnia are not eligible to participate in this study. Also, subjects known to be allergic or sensitive to narcotic drugs, pain killers or drugs used for insomnia are not eligible to participate in this study. Subjects that suffer from hypertension , seizures, bleeding disorders, lung disease or any kind of cardiac condition are not eligible to participate in this study. If you are not eligible to participate in this study, you will be informed.

• **Study Number One: Day 1**. The studies will be conducted in the CRC suite at the Weiler Hospital of the Albert Einstein College of Medicine (1825 Eastchester Road, Room 2S42, Bronx, NY 10461).

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You will be admitted to the Weiler Hospital of the Albert Einstein College of Medicine (1825 Eastchester Road, Room 2S42, Bronx, NY 10461) the evening prior to the study, and a variable-dose infusion of insulin will be initiated at 10:00 PM via a peripheral vein and will continue overnight. The infusion rate of insulin will be adjusted according to hourly plasma glucose, to assure a gradual normalization of plasma glucose levels. At 7:00 AM you will be transferred to the CRC-study room (Room 2S-42) to conduct the study. The study will begin at 7:30 AM. One catheter will be inserted in your arm for intravenous (IV) administration of medicines and a second IV catheter in the other arm for blood drawing. This arm will be kept in a heating device maintained at 55° C (131º F). You will continue to receive basal insulin infusion and a variable infusion of 20% dextrose in order to maintain your plasma glucose at basal levels during the whole duration of the study.

At 9:00 AM you will receive an infusion of morphine for 2 hours. At the end of this two hour period you will receive a snack and wait for two hours. At the end of these two hours of waiting you will again receive an infusion of morphine for 2 hours. Small amounts of blood will be drawn every 30-minutes.At this point, you will receive a meal and will be escorted back to the Hospital room to receive a variable-dose infusion of insulin for the rest of the day and overnight.

The total amount of blood drawn during the study will be 100 ml (about 20 teaspoons).

During this study you may receive potassium chloride supplement tablets in order to prevent lowering of blood potassium levels which may happen during the infusion of insulin. The maximal amount of potassium chloride you could receive in one day will be 80 mEq and maximal amount you could receive in a single dose is 40mEq.

Day 2. The next morning at 7:00 AM you will be transferred to the CRC-study room (Room 2S-42) to conduct the day 2 study. The study will begin at 7:30 AM. One catheter will be inserted in your arm for intravenous (IV) administration of medicines (glucose insulin and glucose tracer) and a second IV catheter in the other arm for blood drawing. This arm will be kept in a heating device maintained at 55° C (131º F).

Your blood sugar will be maintained at normal levels for 2 hours and then lowered gradually (over 4 hours) to 60 mg/dl. A glucose tracer substance will be infused in small amounts continuously throughout the study. Small amounts of blood will be drawn every 5-minutes. The total amount of blood drawn during the study will be 220 ml (about 45 teaspoons). At the end of the study, all infusions will be stopped and you will be given a meal. You will restart your regular insulin regimen and will be discharged home.

• **Study Number Two:** The second study will take place at least six weeks after the previous study. It will be identical to the first study, with the exception that on Day 1 you will receive a small infusion of epinephrine (instead of morphine). Day 2 study will be identical to above.

• **Study Number Three**: The third study will take place at least six weeks after the previous study. It will be identical to the first study, with the exception that on Day 1 you will receive a small infusion of epinephrine and morphine. Day 2 study will be identical to above.

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• **Study Number Four:** The fourth study will take place at least six weeks after the previous study. It will be identical to the first study, with the exception that on Day 1 you will receive a small infusion of saline (instead of morphine or/and epinephrine). Day 2 study will be identical to above.

WHAT ELSE DO I HAVE TO DO?

• You must tell the research study doctor about any past and present diseases or allergies you are aware of and about all medications you are taking including over-the-counter remedies and nutritional supplements or herbs.
• Drugs may cause a reaction that, if not treated promptly, could be life-threatening. It is important that you report all symptoms, reactions and other complaints to the research study doctor.
• If you think you have become pregnant, contact your research study doctor immediately.
• You may carry out all your normal daily activities.

WHAT ARE THE POSSIBLE SIDE EFFECTS, DISCOMFORTS, RISKS OR INCONVENIENCES I CAN EXPECT FROM BEING IN THIS RESEARCH STUDY?

MOST COMMON:

• Intravenous Catheter –The intravenous catheter may cause local irritation and sometimes local infection. Also, the insertion of the catheter is associated with a small risk of local bruising. Blood drawn - The total amount of blood drawn during the two day's procedure is 320 ml (65 teaspoons, less than that donated at a blood bank), and will be replaced with intravenous fluid.

COMMON:

• Hypoglycemia (low blood glucose) - may cause you to feel shaky, sweaty, and nervous or to experience heart pounding. However, the degree of blood sugar lowering is mild and a physician and a nurse will be watching you during the whole procedure. If any symptoms are severe enough such that you can't tolerate them, the study will be stopped. Once the insulin infusion is stopped, blood sugar levels return to normal very rapidly (within minutes). Your blood sugar levels will be continuously monitored throughout this study to ensure it remains within acceptable levels, and additional glucose can be given intravenously at anytime if necessary.

RARE:

• Morphine infusion may cause respiratory depression, nausea, vomiting, constipation, dry mouth, low blood pressure, drowsiness, sedation, agitation, thinking disturbances, and paranoia. We will continuously check your breathing, pulse oximetry, end-tidal CO2, blood pressure and EKG. We will also continuously check your neurological and psychological status. Although the dose of morphine proposed to be administered is not likely to produce side effects, naloxone (antidote to morphine overdose) will available for rapid administration.

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Epinephrine infusion may cause shortness of breath, increased blood pressure, palpitations, irregular heart rate, paleness, excessive sweating, shakiness, nervousness, headache, nausea and vomiting. We will continuously monitor your heart rate, EKG, blood pressure, pulse oximetry, and end-tidal CO2. Epinephrine infusion will be discontinued with the appearance of any side effect.

Glucose tracer (deuterated glucose) is a non-radioactive substance and there is no known risk associated with its infusion.

Potassium chloride tablets may cause stomach upset (such as nausea, vomiting, diarrhea, abdominal pain, discomfort) and extremely rarely they can lead to stomach or bowel ulceration, bleeding, perforation, or obstruction

In addition to the risks listed above, there is always the possibility that you will have a reaction that is currently not known and not expected. Your participation in this study may be discontinued at the discretion of the investigator if you are unable to comply with the study requirements or if in the investigator's opinion this is in your best interest.

PREGNANCY AND IMPREGNATION DURING THIS STUDY

• Pregnant women or women planning to become pregnant, and women who are breast feeding are not eligible to participate in this study because the study involves infusion of morphine and epinephrine that may be dangerous during pregnancy.
• Women of childbearing age will be administered a pregnancy test. An additional pregnancy test will be performed in the morning before each study.

ARE THERE LIKELY TO BE ANY BENEFITS TO TAKING PART IN THIS RESEARCH STUDY?

• This study will be of no direct benefit to you. This study may result in a better understanding of how the body reacts to low blood sugar. Eventually, this information may help researchers to identify new treatment strategies for diabetes mellitus.

WHAT OTHER CHOICES DO I HAVE IF I DO NOT TAKE PART IN THIS RESEARCH STUDY?

• You may choose not to participate in this study.
• Your participation in this study is voluntary. You may be a participant in it only if you wish, and you may withdraw from the study at any time.

WILL I BE PAID FOR BEING IN THE STUDY?

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• You will receive payment for time and inconvenience associated with the study. Subjects have the option to choose between clincard greenphire payment or checks. Clincards are typically loaded with compensation within 24-48 business hours from the day of your study. You will not be reimbursed for child care expenses but only for travel expenses. For completion of each study, you will receive $400. If you choose to withdraw or cannot complete the study, the compensation will be pro-rated based on the time spent, with a minimum payment of $50 for participation in the testing procedures. For example, if you complete only the first day, you will receive $50. A social security number is required. It will be kept confidential.

WHO MAY SEE MY RECORDS?

• The research records will be kept private and your name will not be used in any written or verbal reports.
• Your research records may be inspected by members of the research team, the sponsor(s), and other institutions that participate in this study. These are: The National Institutes of Health, The National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK), Albert Einstein College of Medicine and Montefiore Medical Center, Office of Human Research Protection (OHRP), and the Federal Drug Administration (FDA). These groups have been requested to maintain confidentiality. Your records may also be inspected by the human research committee of the Einstein Institutional Review Board (IRB).
• The research records will be kept in a secured manner and computer records will be password protected in the Albert Einstein College of Medicine Clinical Research Center (CRC).
• The Clinical Research Center staff, as well as the research personnel authorized by the researcher will have access to these records.
• The Office of Human Research Protections (OHRP) may also review your research study records.
• A description of this clinical trial will be available on http://www.clinicaltrials.gov/, as required by U.S. Law. This Web Site will not include information that can identify you. At most, the Web Site will include a summary of the results. You can search this Web Site at any time.
• All of these groups have been requested to keep your name private.

WHAT HAPPENS IF I AM INJURED BECAUSE I TOOK PART IN THIS RESEARCH STUDY?

If there is a physical injury as a result of this research, only immediate, essential, short-term medical treatment as determined by the participating hospital, will be available for the injury without charge to you personally.

• No monetary compensation will be offered.
• You are not waiving any of your legal rights by signing this informed consent document
• If additional treatment is required as a result of a physical injury related to the research, necessary medical treatment will be provided to you and billed to your insurance company or to you as part of your medical expenses.
• Immediately report any discomforts, problems or injuries you experience during the course of your participation in the study to Dr. Hawkins at (718) 430-3186. .

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WILL THERE BE ANY COSTS TO ME?

• There will be no costs to you for participating in this study.

WHO CAN ANSWER MY QUESTIONS ABOUT THE STUDY?

Researcher's Name: Meredith A. Hawkins, M.D. Office Address: 1300 Morris Park Avenue, Belfer Building Room 702, Bronx, NY 10461
Office Phone: 718-430-3186

• If any questions arise related to this research project, or you believe you have any injury related to this study, you can call the researcher above.
• You may also call the Study Coordinator at 718-430-2903.
• If you have questions regarding your rights as a research subject, you may also call the Manager of Einstein IRB at (718) 430-2253, Monday through Friday between 9 AM and 5 PM.

CAN I BE ASKED TO STOP PARTICIPATING IN THIS STUDY BEFORE THE STUDY IS FINISHED?

You may be asked to stop participating in this study before the study finished if:

• You fail to follow instructions given to you by the research study doctor.
• You become pregnant or wish to become pregnant.
• Recruitment goals are not met.

WHAT IF NEW INFORMATION BECOMES AVAILABLE?

• If the research study doctor obtains new information that might lead you to change your mind about continuing in this study, the research study doctor will tell you about it.

MAY I STOP THE STUDY AT ANY TIME?

• Your participation in this study is voluntary, and you may withdraw from the study at any time without giving a reason.
• If you decide to withdraw after receiving the study drug, you should talk with the research study doctor to see how best to complete the withdrawal process.
• If you agree to participate and withdraw at a later time, some of your information may have already been entered into the study and that will not be removed.
• Your treatment by doctors and staff at the institution(s) involved in this study, now and in the future, will not be affected in any way if you agree to participate and withdraw later.

WHAT ARE MY RIGHTS IF I TAKE PART IN THIS RESEARCH STUDY?

• Your participation in this study is voluntary.
• You do not waive any of your legal rights by participating in this research study.

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• Your treatment by doctors and staff at the institution(s) involved in this study, now and in the future, will not be affected in any way if you refuse to participate or if you enter the study and withdraw later.

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Informed Consent Signature Page

The following is a list of items we discussed about this research study. If you have any questions about any of these items, please ask the person who is discussing the study with you for more information before agreeing to participate.

- What the study is about.
- What I must do when I am in the study.
- The possible risks and benefits to me.
- Who to contact if I have questions or if there is a research related injury.
- Any costs and payments.
- I can discontinue participating in the study at any time without penalty.
- Other choices.
- All written and published information will be reported as group data with no reference to my name.
- If there is a schedule explaining how the study medicines are to be taken, I will be given the time schedule.
- I have been given the name of the researcher and others to contact.
- I have the right to ask any questions.

Printed Name of Participant	Signature of Participant	Date	Time
Printed Name of Person Conducting the Informed Consent Process	Signature of Person Conducting the Informed Consent Process	Date	Time