CONSENT FORM

A randomized double blinded study to examine the use of
N-acetyl cysteine for the prevention and treatment of HAAF in patients with type 1 diabetes.

Diphenhydramine pretreatment study

(June 15, 2017)

You are invited to participate in a study designed to investigate the effects of N-acetyl cysteine on the prevention and treatment of impaired awareness of hypoglycemia in patients with type 1 diabetes. You were selected as a possible participant because you are a healthy volunteer. We ask that you read this form and ask any questions you may have before agreeing to be in the study. This study is being conducted by:

Elizabeth R. Seaquist, M.D.
Department of Medicine
(612) 626-4833
University of Minnesota Medical School
Minneapolis, MN 55455

Why is this study being done?
Low blood sugar is also called hypoglycemia. Usually, it is mild and can be treated quickly and easily by eating or drinking a small amount of a sugar-rich food. If low blood sugar is left untreated, it can get worse and cause confusion, clumsiness or fainting. Severe hypoglycemia can lead to seizures, coma, and even death.

Some people with diabetes do not have early warning signs of low blood sugar. This condition is called hypoglycemia unawareness. It happens when the body stops reacting to low blood sugar levels and the person does not realize that they need to treat their hypoglycemia. This can lead to more severe and dangerous hypoglycemia.

The purpose of this early study is to see if a drug called N-acetyl cysteine should be studied more in people with Type I diabetes and hypoglycemia unawareness, impaired awareness of hypoglycemia, or hypoglycemia associated autonomic failure (HAAF). This study will show whether N-acetyl cysteine (NAC) could be used to prevent and treat hypoglycemia unawareness.

How long will the study last?
Each person in this study will participate for approximately 12 weeks. The study will be done in two parts separated by 8 weeks.

What is involved in the study?
If you agree to participate in this study, this is what you will be asked to do:

<u>Screening visit</u>
At this visit, you will be asked questions about your medical history to make sure you are eligible to be in this study. You will also have some blood collected for measurement of a hemoglobin A1c to make certain you do not have diabetes. If you are a female who could become pregnant, a pregnancy test will also be done. The amount of blood that will be collected at this visit is approximately three teaspoons. This visit is estimated to last approximately one hour.

Part one

On day one, you will be asked to come to the Masonic Clinical Research Unit (MCRU) by 7AM after fasting overnight. Two IV catheters will be placed in your arms. This will allow for giving insulin, glucose and potassium, N-acetyl cysteine or saline during the test and for the collection of blood samples. The arm used for blood drawing may be placed in a heated blanket for the duration of study to speed up the flow of blood through vein and for easy withdrawing of blood.

30 minutes after the catheters are in place, you will be given an intravenous infusion of diphenhydramine (common name Benadryl) followed by 5 hour intravenous infusion of NAC or saline. Which drug you will be given will be determined in the pharmacy and neither you nor the study personnel will know which you have been assigned. The assignment will be randomly made, like the flip of a coin. 30-90 minutes after the start of the NAC or saline, infusions of insulin and potassium will be started. Insulin is a hormone that your body makes naturally and it causes your blood sugar to decrease. Potassium is a salt-like substance that is present in the blood. Your glucose will be checked every five minutes throughout the study and we will let it fall to a value of 50 mg/dl. Once it gets that low we will keep it there by infusing glucose. We will continue the insulin and potassium infusions for 120 minutes and then give you glucose to return the sugar to normal. During the study blood will be drawn every 5 minutes for measurement of glucose and other hormones and chemicals. You will also be asked to complete a questionnaire about any symptoms of hypoglycemia you may be experiencing at the start of the day and at the end of the hypoglycemic period. You will be asked about whether you have symptoms of itching, tingling, swelling of your mouth or tongue, or are having trouble breathing since these are rare side effects of NAC.

120-240 minutes after the insulin infusion is stopped, infusions of insulin and potassium will be started again. Your glucose will be checked every five minutes throughout the study and we will let it fall to a value of 50 mg/dl. Once it gets that low we will keep it there by infusing glucose. We will continue the insulin and potassium infusions for 120 minutes and then give you glucose to return the sugar to normal. During the study blood will be drawn every 5 minutes for measurement of glucose and other hormones and chemicals. You will also be asked to complete a questionnaire about any symptoms of hypoglycemia you may be experiencing at the start of the day and at the end of the hypoglycemic period. You will be asked about whether you have symptoms of itching, tingling, swelling of your mouth or tongue, or are having trouble breathing since these are rare side effects of NAC. At the completion of the study, you will be given a meal and then allowed to leave the research center with the plan to return the next morning.

The following morning (day 2) you will arrive at the MCRU by 7 AM after fasting overnight. Two IV lines will be placed in your arms and infusions of insulin and potassium will be started. Your glucose will be checked every five minutes throughout the study and we will let it fall to a value of 45 mg/dl over 120 minutes. We will stop the insulin and potassium infusions and give you glucose to return the sugar to normal. During the study blood will be drawn every 5 minutes for measurement of glucose and other hormones and chemicals. You will also be asked to complete questionnaires about any symptoms of hypoglycemia you experience during the hypoglycemic period. At the end of the study you will be given a meal, and you will then be sent home.

Part two

Part two will be done approximately 8 weeks later, exactly like part one, except if you were given NAC during part one you will now be given saline. If you were given saline during part one, you will now be given NAC.

Risks and Benefits of Being in the Study:
The study has several risks, which are understood, and measures to minimize the risks have been established:

1. Infusions/blood drawing: Occasionally individuals may have some bruises afterwards where the catheter was inserted. Some people experience a burning or cramping in their arm when glucose or potassium is infused. This feeling goes away when we reduce the rate at which the substance is given to you. Rarely an individual may experience inflammation of the vein (phlebitis). If this happens, your arm may feel sore for a couple of weeks and your vein may feel lumpy. These symptoms usually go away with local heat and elevation of the extremity. Participants will be observed closely for these complications, and if these complications occur, care will be promptly and appropriately administered. The maximum amount of blood that will be collected during the study will be 30-40 tablespoons. We will not allow you to be in the study if you have given or expect to give a similar amount of blood in the month before or after the research procedures.
2. Hypoglycemia (low blood sugar): Symptoms of hypoglycemia include sweating, shakiness, confusion, increased heartbeat and feeling "low". It is reversed within minutes by stopping the insulin infusion and by raising your blood sugar by increasing the rate of glucose infusion. When you are participating in the low blood glucose protocol of the study we expect you will develop some of these symptoms during the study. To be certain that your blood sugar level does not drop less than 30 mg/dl, we will check your blood every five minutes during the study and adjust the amount of sugar we give you by vein to keep your blood sugar at the correct level. If the blood sugar drops below 20 mg/dl, confusion, seizures, coma or abnormalities in heart rhythm can occur. With careful monitoring, it is very unlikely that your blood sugar will drop to less than 30 mg/dl.
3. N-acetyl cysteine: NAC is a therapy that has long been FDA approved for the treatment of acetaminophen overdose is available as a nutritional supplement, and has been used to treat a variety of human conditions. The most common adverse reactions (incidence > 2%) are rash, facial flushing and itching. Less common reactions include nausea and vomiting. These reactions usually occur 30-60 minutes after initiating the infusion, and often resolve spontaneously despite continued infusion of NAC. Serious anaphylactic reactions, including death in a patient with asthma, have been reported in patients given intravenous NAC. These reactions include symptoms such as rash, hypotension, wheezing and/or shortness of breath. To make sure you are tolerating the NAC, we will ask you about symptoms like itching, nausea, tingling or swollen in your mouth or tongue, and breathing four times during the infusion. If you develop symptoms the infusion will be stopped and the doctor will monitor you until the symptoms are gone. If the symptoms are severe, we will have a kit at the bedside that can treat allergic reactions (medications we have available include diphenhydramine, ondansetron, epinephrine) or we can call upon the emergency help available in the hospital where the MCRU is located.
4. Diphenhydramine: Diphenhydramine will be given immediately before you are given the NAC or saline infusion to minimize your chance of developing side effects to the NAC. This drug is commonly used to treat allergies and is available over the counter. Side effects of diphenhydramine include drowsiness, stomach upset, dizziness and headache.

There are no direct benefits of participation to you other than the satisfaction you may have in helping us answer important as yet unanswered questions about human glucose metabolism.

Research Related Injury
In the event that this research activity results in an injury, treatment will be available, including first aid, emergency treatment, and follow-up care as needed. Care for such injuries will be billed in the ordinary manner to you or your insurance company. If you think that you have suffered a research related injury, let the study physicians know right away.

Compensation:
You will be paid $25 for the screening visit, $150 per day for each day of Part one you complete, and $200 for each day of Part Two you complete to cover travel expenses and time lost from work for each day of study, up to a total of $725. Because the amount of money paid to you may exceed $600, we will be obligated to ask you to complete a W9 tax form. If the money paid to you does exceed $600 in a calendar year, this information will be reported to the Internal Revenue Service (IRS), and you will be issued a Form 1099-MISC from the University of Minnesota to use when completing your personal income tax.

Confidentiality:
Efforts will be made to limit the use and disclosure of your personal information, including research study and medical records, to people who have a need to review this information. We cannot promise complete privacy. Organizations that may inspect and copy your information include the IRB and other representatives of this institution, including those that have responsibilities for monitoring or ensuring compliance.

The sponsor, monitors, auditors, the IRB, the University of Minnesota Research Compliance Office and other University compliance units, the US Office of Research Integrity (ORI), the US Office for Human Research Protections (OHRP), and the US Food and Drug Administration (FDA) may be granted direct access to your medical records to conduct and oversee the research. By signing this document you are authorizing this access. We may publish the results of this research. However, we will keep your name and other identifying information confidential.

A description of this clinical trial is available at 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.

Protected Health Information (PHI):
Your PHI created or received for the purposes of this study is protected under the federal regulation known as HIPAA. Refer to the attached HIPAA authorization for details concerning the use of this information.

Voluntary Nature of the Study:
Your decision whether or not to participate will not affect your current or future relations with the University. If you decide to participate, you are free to withdraw at any time without affecting those relationships.

New Information:
If during the course of this research study, there are significant new findings discovered which might influence your willingness to continue, the researchers will inform you of those developments.

Contacts and Questions:
The researcher conducting this study is Elizabeth R. Seaquist MD. You may ask any questions you have now. If you have questions later, you may contact her at (612) 624-9176.

This research has been reviewed and approved by an Institutional Review Board (IRB) within the Human Research Protections Program (HRPP) at the University of Minnesota. To share feedback privately with the HRPP about your research experience, call the Research Participants' Advocate Line at 612-625-1650 or go to www.irb.umn.edu/report.html. You are encouraged to contact the HRPP if:

- Your questions, concerns, or complaints are not being answered by the research team.
- You cannot reach the research team.

- You want to talk to someone besides the research team.
- You have questions about your rights as a research participant.
- You want to get information or provide input about this research.

Future Contact for Other Research Studies:
The following research activities are optional, meaning that you do not have to agree to them in order to participate in the research study. Please indicate your willingness to participate in these optional activities by placing your initials next to each activity.

I agree	**I disagree**	
_____	_____	The researchers may contact me in the future to see whether I am interested in participating in other research studies conducted by the Division of Diabetes and Endocrinology at the University of Minnesota.

Statement of Consent:
I have read the above information, asked questions and have received answers, and I consent to participate in the study.

You will be given a copy of this form to keep for your records.

Signature: _____ Date: _____

Signature of Investigator: _____ Date: _____