IRB NUMBER: 2018-9208
IRB APPROVAL DATE: 05/17/2019
IRB EXPIRATION DATE: 05/16/2020

ALBERT EINSTEIN COLLEGE OF MEDICINE
MONTEFIORE MEDICAL CENTER

DOCUMENTATION OF INFORMED CONSENT AND HIPAA AUTHORIZATION

Introduction
You are being asked to participate in a research study called **Novel Approach for the Prevention of Hypoglycemia Associated Autonomic Failure (HAAF).** Your participation is voluntary -- it is up to you whether you would like to participate. It is fine to say "no" now or at any time after you have started the study. If you say "no," your decision will not affect any of your rights or benefits or your access to care.

The researcher in charge of this project is called the "Principal Investigator." Her name is Dr. Meredith A. Hawkins. You can reach Dr. Hawkins at: **Office Address: 1300 Morris Park Avenue, Bronx, NY 10461** **Telephone #: (718)-430-3186** For questions about the research study, or if you believe you have an injury, contact the Principal Investigator or the IRB.	The Institutional Review Board (IRB) of the Albert Einstein College of Medicine and Montefiore Medical Center has approved this research study. The IRB # is in the stamp in the upper right hand corner. If you have questions regarding your rights as a research subject you may contact the IRB office at 718-430-2253, by e-mail at irb@einstein.yu.edu, or by mail: Einstein IRB Albert Einstein College of Medicine 1300 Morris Park Ave., Belfer Bldg #1002 Bronx, New York 10461
Support for this research study is provided by **NIH**	

Why is this study being done?

The purpose of this study is to understand how and why the body reacts to low glucose (blood sugar), and to find ways to improve the treatment for diabetes.

In this research study, we will test the effects that intranasal (inhaled through the nose) naloxone (an FDA approved drug used to treat morphine overdose, also called NARCAN) has on the body's ability or failure to counter-regulate (raise) blood sugar levels back to within range of normal, healthy levels. The information obtained from your studies will be compared to information obtained from patients with type 1 diabetes, thus enabling us to identify the specific problems patients with type 1 diabetes have.

Why am I being asked to participate?

You are being asked to participate in this study as a healthy subject (control).

EINSTEIN
Albert Einstein College of Medicine
IRB NUMBER: 2018-9208
IRB APPROVAL DATE: 05/17/2019
IRB EXPIRATION DATE: 05/16/2020

How many people will take part in the research study?

15 healthy non-diabetic subjects will be enrolled (ranging in age from 21 to 55 years old) to this aim of the study.

How long will I take part in this research?

It will take you approximately 3-5 months to complete this research study. During this time, we will ask you to come for two 2-day study visits at least 1 month apart to Weiler Hospital and the Albert Einstein College of Medicine. Each of these two 2-day study visits will consist of two consecutive days - Day 1 and Day 2. Each time, you will go home at the end of Day 1 and will be asked to come back on the morning of Day 2. Depending on the results of this study, you may be eligible to participate in future studies. Participation is voluntary, and you will be re-consented if applicable. These future studies could take up to 6 months to complete

What will happen if I participate in the study?

The Screening Visit will take about 1.5 hours. During this visit, we will do some tests and procedures to see if you eligible to take part in this research study. The study doctor will review the results of these tests and procedures. At this visit we will:

- Ask you about your medical history
- Give you a physical exam, including height, weight, and "vital signs" (blood pressure, temperature, heart and breathing rates)
- Draw a blood sample
- Take an EKG
- Ask you for a urine sample
- Test your urine for certain drugs
- Test your urine for pregnancy, if you are a female able to become pregnant. Pregnant women cannot take part in this research study.

To obtain the blood sample, we will wipe the skin on your arm with alcohol to clean it. Then, we will insert a small needle into a vein. 5 tubes of blood will be drawn, which is about 7 teaspoons.

If you are not eligible, you will be informed by phone or in writing and records of the evaluation will be forwarded to you.

This research study will compare intranasal naloxone to placebo nasal spray. The placebo looks exactly like NARCAN (naloxone), but contains no drugs. During this study, you may get a placebo instead of NARCAN first. Placebos are used in research studies to see if the results are due to the study drug or due to other reasons.

If you are eligible for the study, we will assign you by chance (like a coin toss) to first receive either naloxone or placebo. You and the study doctor cannot choose your study order.

A description of this clinical trial will be available on 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.

As part of this study we may review your medical records, if available, and put the information we collect in our research records.

EINSTEIN Albert Einstein College of Medicine
IRB NUMBER: 2018-9208
IRB APPROVAL DATE: 05/17/2019
IRB EXPIRATION DATE: 05/16/2020

Study Details:

• Your participation will involve two 2-day study visits which will be at least 4-6 weeks apart. Each 2-day study visit will last two days, and you will go home between the days. There will be no specific order in choosing to perform one study visit or another. This means that although study procedures are described below as taking place during **Study Visit Number One** and **Study Visit Number Two**, you may actually undergo procedures described in Study Visit Number Two before those described in Study Visit Number One, or vice versa.

• Subjects that suffer from hypertension, seizures, bleeding disorders, lung disease, or any kind of cardiac condition are not eligible to participate in this study.

• **Please note: subjects currently using narcotic or sedative drugs are not eligible to participate in this study. A thorough medical history, including information on opiate usage, and a urine toxicology screen will be collected to ensure that ineligible participants are not enrolled. If you are not eligible to participate in this study, you will be informed.**

Study Visit 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).
- You will be asked to arrive at approximately 8:00 AM in the morning of the study at the CRC. We ask that you arrive fasting to the CRC suite in Weiler Hospital. This means that you shouldn't eat or drink anything except for water after 10 PM the night before your visit. You will be given a pregnancy test (for women of child-bearing age) and a urine drug test before we begin any study procedures. If either returns positive, you will be withdrawn from the study. One catheter will be inserted in your arm for intravenous (IV) administration of study drugs and a second IV catheter in the other arm for blood drawing. In order to maintain this intravenous catheter open, normal saline mixed with a small amount of heparin will be infused continuously at a slow rate. Additionally, the insulin will be infused with a small amount of human albumin to prevent the insulin from sticking to the tube. This arm will be kept in a heating device maintained at 55° C (131° F).
- At approximately 9:00 AM, you will receive infusions of insulin and dextrose in order to gradually lower your blood sugar to a mild state of hypoglycemia (54 mg/dl). You will receive a spray of the NARCAN® Nasal Spray as aerosolized particles twice during each hypoglycemia episode; at the start of the insulin infusion in one nostril, and again after 60 minutes in the other nostril. Throughout this two-hour period, your blood sugar will be kept at 54 mg/dl. 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 infusions of insulin and dextrose to gradually lower your blood sugar to 54 mg/dl for another two hours. You will receive another spray of the NARCAN® Nasal Spray in one nostril at the start of the insulin infusion and again in the other nostril after 60 minutes. Your blood sugar will be kept at 54 mg/dl throughout this second two-hour period.
- You will receive potassium chloride oral powder (Klor-Con) dissolved in water in order to prevent lowering of blood potassium levels, which may happen during the infusion of insulin. You will receive 40 mEq of potassium chloride at the beginning of each insulin infusion, with a total dose of 80 mEq for Day 1.

EINSTEIN Albert Einstein College of Medicine
IRB NUMBER: 2018-9208
IRB APPROVAL DATE: 05/17/2019
IRB EXPIRATION DATE: 05/16/2020

- Small amounts of blood will be drawn as often as every 5 minutes throughout each two-hour period. At the conclusion of the study, you will receive a meal and will be monitored in the CRC study room for approximately one hour prior to being discharged. Day 1 of each study visit will end at approximately 4 PM. You will be asked not to eat after 10 PM on Day 1.
- The total amount of blood drawn during day 1 will be approximately 180 mL (36 teaspoons).

Study Visit Number One: Day 2

- The next morning, you will be asked to arrive at approximately 8:00 am at the CRC to conduct Day 2 of the study visit. We ask that you also arrive to this visit fasting. This means that you shouldn't eat or drink anything except for water after 10 PM the night before this visit One catheter will be inserted in your arm for intravenous (IV) administration of study drugs (glucose, insulin and glucose tracer) and a second IV catheter in the other arm for blood drawing. In order to maintain this intravenous catheter open, normal saline mixed with a small amount of heparin will be infused continuously at a slow rate. Additionally, the insulin will be infused with a small amount of human albumin to prevent the insulin from sticking to the tube. This arm will be kept in a heating device maintained at 55° C (131° F).
- Your blood sugar will be maintained at normal levels for 2 hours and then reduced gradually to 54 mg/dL. A non-radioactive glucose tracer substance will be infused (given to you through your vein) in small amounts continuously throughout the study. Small amounts of blood will be drawn as often as every 5 minutes. The total amount of blood drawn during Day 2 will be approximately 180 ml (about 36 teaspoons).
- You will receive potassium chloride oral powder (Klor-Con) dissolved in water, again, in order to prevent lowering of blood potassium levels, which may happen during the infusion of insulin. You will receive 40 mEq of potassium chloride at the beginning of the insulin infusion on Day 2.
- At the end of the study, all infusions will be stopped. You will receive a meal and will be monitored in the CRC study room for approximately one hour prior to being discharged home.
- The total amount of blood drawn over the two days is approximately 360 mL, less than what you would donate at a blood blank.

Study Visit Number Two: The second 2-day study visit will take place 4-6 weeks after the first 2-day study visit. It will be identical to the first 2-day study visit, with the exception that on Day 1 you will receive a placebo saline nasal spray in each nostril during both episodes of hypoglycemia instead of the NARCAN® Nasal Spray. We will use a placebo to help us see if taking NARCAN® Nasal Spray is better than taking nothing at all on your body's ability to raise your blood sugar level back to within a normal range following hypoglycemia (low blood sugar). Day 2 of study visit number two will be identical to the one above.

Genetic Testing

This study will not involve genetic research or genetic testing.

EINSTEIN Albert Einstein College of Medicine
IRB NUMBER: 2018-9208
IRB APPROVAL DATE: 05/17/2019
IRB EXPIRATION DATE: 05/16/2020

Specimen Banking (Future Use and Storage)

We will store your specimens and information about you in a "biobank", which is a library of information and specimens (tissue and blood) from many studies. These specimens and information cannot be linked to you. In the future, researchers can apply for permission to use the specimens and information for new studies to prevent, diagnose, or treat disease, including genetic research. Your specimens and information may be kept for a long time, perhaps longer than 50 years. If you agree to the future use, some of your de-identified genetic and health information (not linked to you) may be placed into one or more scientific databases. These may include databases maintained by the federal government.

You can choose not to participate in the biobank and still be part of the main study and this will not affect your treatment at this facility.

INITIAL ONE (1) OF THE FOLLOWING OPTIONS

_____ I consent to have my specimens and information about me used for future research studies.

_____ I do NOT consent to have my specimens and information about me used for future research studies. Information about me will be kept as long as required by regulations and institutional policy, but will not be used for future studies.

Will I be paid for being in this research study?

• You will receive payment for time and inconvenience associated with the study. You will be paid with a Clincard Greenphire payment. **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 two day Study Visit, you will receive $400. You will receive $50 after the first day of each Study Visit and $350 after the second day of each Study Visit. This aim features two 2-day study visits. Therefore, if you complete this study aim you will receive a total of $800. If you choose to withdraw or cannot complete the study because you feel unwell during the study, or the study needs to be stopped due to a logistical or technical issue, the compensation will be pro-rated based on the time spent. Additionally, you will be drug-tested upon arrival before we begin any study procedures during each visit. If the drug test is positive, you will be withdrawn from the study. A social security number is required. It will be kept confidential.

Participants in this study may receive more than $600 in a calendar year for their participation. The IRS requires that we report this as income. Therefore, you must provide your social security number if you wish to receive these payments.

Some researchers may develop tests, treatments, or products that are worth money. You will not receive payment of any kind for your specimens and information or for any tests, treatments, products, or other things of value that may result from the research.

Will it cost me anything to participate in this study?

There will be no cost to you to participate in the study.

What will happen if I am injured because I took part in this study?

If you are injured 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.

In addition to seeking appropriate medical attention, please immediately report any discomforts, problems, or injuries you experience during the course of your participation in the study to Dr. Meredith Hawkins 718-430-2903.

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.
- If you do not feel well at any time, call your doctor or the research study doctor immediately.
- 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.

Confidentiality

The researchers and study staff follow federal and state laws to protect your privacy. This part of the consent form tells you what information about you may be used and shared in the research described in this form. You do not have to sign this form but, if you do not, you may not participate in the research.

The health information that we may use or disclose for the research described in this form includes information from your entire medical record, such as your name, phone number, email, medical diagnoses, dates, test results, social security number, medical record numbers, etc.

Your information and research records will be kept confidential. Your study information will be kept as long as they are useful for the research described in this form.

The only people who can see your research records are:

- the research team and staff who work with them
- the organization that funded the research
- groups that review research (the Einstein IRB, and the Office for Human Research Protections, and the US Food and Drug Administration)

The purposes of these uses and disclosures are to (1) conduct the study and (2) make sure the study is being done correctly. The information covered under this form may no longer be protected by federal privacy laws (such as HIPAA) once disclosed, and those persons who

EINSTEIN Albert Einstein College of Medicine
IRB NUMBER: 2018-9208
IRB APPROVAL DATE: 05/17/2019
IRB EXPIRATION DATE: 05/16/2020

receive your health information may share your information with others without your additional permission. All of these groups have been asked to keep your information confidential.

Medical information collected during the research, such as test results, may be entered into your Montefiore electronic medical record and will be available to clinicians and other staff at Montefiore who provide care to you.

To maintain the integrity of this research study, you generally will not have access to your research-related personal health information. If it is necessary for your care, your research-related health information will be provided to you or your physician.

Some of your blood samples may be sent to Vanderbilt University for analyses of hormone levels. Involvement of Vanderbilt University will be limited only to performing the analysis of blood samples, they will not receive any identifying information about you. Thus, it will not be possible for Vanderbilt to link these samples to any of your records.

Certificate of Confidentiality
As a way to protect your privacy, we have obtained a Certificate of Confidentiality from the National Institutes of Health, which is funding this study. If information from this study was requested or subpoenaed by government agencies or the courts, we will use the Certificate to attempt to legally refuse to provide it. This is rare – in only a few cases did researchers have to use the Certificate, and it was honored most of the time, but not every time. There are several kinds of situations that the Certificate does not apply. For example, we are still required to report child abuse and some diseases, and we must make data available to the government for a review or evaluation of our research. The Certificate does not prevent you or a member of your family from voluntarily sharing information. Similarly, if an insurer, employer, or other person obtains your written consent to receive research information, then the researchers may not use the Certificate to withhold that information.

Are there any risks to me?

• **Blood Draw:** Rarely, the vein where we inserted the needle will become sore or red. Sometimes, a temporary harmless "black and blue" may develop. Very rarely, fainting may occur.

• **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.

• **Hypoglycemia/Insulin (low blood glucose):** During the study, we will infuse insulin in order to gradually lower your blood sugar to 54 mg/dL. This may cause you to feel shaky, sweaty, 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 any time if necessary to raise blood sugar.

• **20% dextrose**: Although the infusion of 20% dextrose may be associated with local venous irritation, the infusion of other fluids will reduce the chances of this by reducing the concentration of dextrose.

EINSTEIN Albert Einstein College of Medicine
IRB NUMBER: 2018-9208
IRB APPROVAL DATE: 05/17/2019
IRB EXPIRATION DATE: 05/16/2020

• **Naloxone:** At higher doses, naloxone may cause nausea and vomiting, hypertension, and cardiac arrhythmias. The abrupt reversal of narcotic depression may result in nausea, vomiting, sweating, tachycardia, increased blood pressure, and tremulousness. Intranasal naloxone may be associated with nasal dryness, nasal edema, nasal congestion, and nasal inflammation. All subjects will be screened for opiate usage in order to eliminate the possibility of reversal of narcotic effect. Additionally, monitoring of heart rate and blood pressure will be performed during the studies. Seizures have been reported to occur infrequently after the administration of naloxone; however, a causal relationship has not been established.

• **D2G glucose tracer (deuterated glucose):** D2G is a non-radioactive substance and there is no known risk associated with its infusion.

• **Heparin:** There is a very small risk of bleeding or drop in the number of platelets with heparin infusion. If such reactions occur, the infusions will be stopped, a physician and a nurse will evaluate you, your blood tests will be checked, and you will receive further treatment if medically indicated. Also, there is a very small risk of allergic reaction to heparin, which could manifest with a rash and itchiness, and extremely rarely with swelling, dizziness, low blood pressure, and problems with breathing. In an unlikely event of allergic action, the infusions will be stopped, you will be evaluated by a physician and a nurse, and will receive further treatment for allergic reaction if medically indicated.

• **Human albumin:** There is a very small risk of developing an allergic reaction to albumin, which could manifest with a rash and itchiness, and extremely rarely with swelling, dizziness, low blood pressure and problems with breathing. In an unlikely event of allergic action, the infusions will be stopped, you will be evaluated by a physician and a nurse and will receive further treatment for allergic reaction if medically indicated.

• **Potassium Chloride:** The most common adverse reactions with potassium chloride oral powder (Klor-Con) are nausea, vomiting, flatulence, abdominal pain/discomfort, and diarrhea.

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.

Risks to Women Who Are or May Become Pregnant

The effect of naloxone on an embryo or fetus (developing baby still in the womb), or on a breastfeeding infant, is unknown, and may be harmful. Because of these unknown risks, women cannot take part in this study if they are:

- Pregnant
- Trying to become pregnant
- Breastfeeding or sharing breast milk

New Findings

If we learn any significant new findings during the study that might influence your decision to participate, we will contact you and explain them.

EINSTEIN Albert Einstein College of Medicine
IRB NUMBER: 2018-9208
IRB APPROVAL DATE: 05/17/2019
IRB EXPIRATION DATE: 05/16/2020

Unknown Risks
We have described all the risks we know. However, because this is research, there a possibility that you will have a reaction that we do not know about yet and is not expected. If we learn about other risks, we will let you know what they are so that you can decide whether or not you want to continue to be in the study.

Are there possible benefits to me?

You will not experience any direct benefit personally from participating in this study. We hope that you will participate because the study will generate important information about **type 1 diabetes.**

What choices do I have other than participating in this study?

You can refuse to participate in the study.

Are there any consequences to me if I decide to stop participating in this study?

No. If you decide to take part, you are free to stop participating at any time without giving a reason. This will not affect your care and you will continue to be treated at this facility. However, some of the information may have already been entered into the study and that will not be removed. The researchers may continue to use and share the information they have already collected.

To revoke (take back) your consent and authorization, you must contact the Principal Investigator in writing at the address on page 1 of this form. However, you may first call or speak to the Principal Investigator and she will stop collecting new information about you. If you take back your consent and authorization, you will not be allowed to continue to participate in this research study.

Can the study end my participation early?

We will not let you participate in the study any more if **(1) you become pregnant or want to become pregnant, (2) you fail to follow instructions given to you by the research doctor, (3) you experience adverse reactions to the study drug (4) you test positive on a drug test.** In addition, your participation will end if the investigator or study sponsor stops the study earlier than expected.

Summary of Study Days:

Day 1:

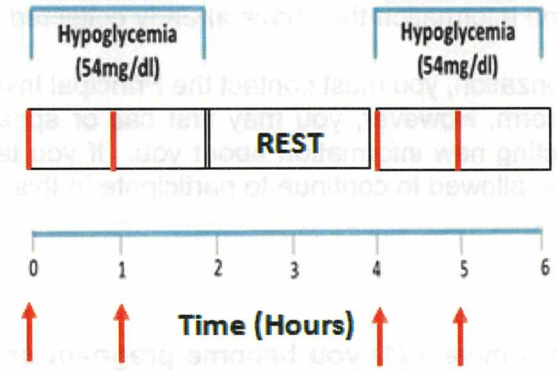
Please arrive at 8 AM, **fasting**, to the CRC suite in Weiler Hospital. Your last meal should be before 10 PM the prior evening. Similar to your previous study visit, we will use insulin to induce 2 episodes of low blood sugar (hypoglycemia), which will be maintained for 2 hours. During the first episode of hypoglycemia, you will receive either intranasal Naloxone (4 mg Narcan spray) or placebo as shown in the diagram below. You will then be allowed to rest for 2 hours, as we allow your glucose (blood sugar) to return to your normal range with glucose tablets taken by mouth as well as intravenous glucose. This will be followed by the second 2-hour episode of low blood sugar (hypoglycemia) as we again administer intranasal Naloxone or placebo, maintaining your blood glucose (blood sugar) at 54 mg/dl. Throughout the study, we will monitor your heart rate, vital signs, and any symptoms of low blood sugar to ensure that you are kept safe and

IRB NUMBER: 2018-9208
IRB APPROVAL DATE: 05/17/2019
IRB EXPIRATION DATE: 05/16/2020

comfortable. We will also take blood samples to measure your glucose and hormone levels throughout the study. After the completion of the second 2-hour episode of low blood sugar, you will be given a full meal, and your vital signs and blood sugar levels will be monitored, to ensure they have returned to baseline. You will then be able to return home.

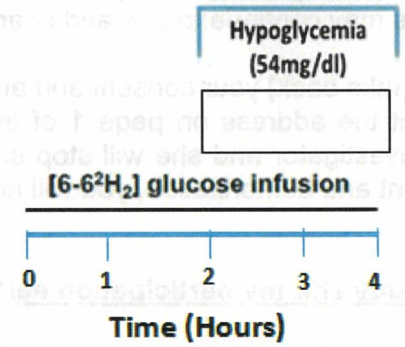
Day 2:

Similar to Day 1, we ask that you arrive at 8 AM, **fasting**, to the CRC suite in Weiler Hospital. Your last meal should be before 10 PM the prior evening. We will give you insulin to induce hypoglycemia (low blood sugar) for 2 hours (see diagram). Further, you will receive a 4-hour infusion of a non-radioactive glucose tracer, which allows us to measure the way your body handles sugar. This will start two hours before any insulin is given. As before, we will monitor your heart rate, vital signs, and any symptoms of low blood sugar, to ensure you are kept safe and comfortable during the study. We will also take blood samples to measure your glucose and hormone levels throughout the study. After the completion of the study, you will be given a full meal, and your vital signs and blood sugar levels will be monitored, to ensure they have returned to baseline. You will then be able to return home.



Intranasal Naloxone OR Placebo Spray

Experimental Protocol on Day 1



Experimental Protocol on Day 2

IRB NUMBER: 2018-9208
IRB APPROVAL DATE: 05/17/2019
IRB EXPIRATION DATE: 05/16/2020

CONSENT TO PARTICIPATE

I have read the consent form and I understand that it is up to me whether or not I participate. I know enough about the purpose, methods, risks and benefits of the research study to decide that I want to take part in it. I understand that I am not waiving any of my legal rights by signing this informed consent document. I will be given a signed copy of this consent form.

Printed name of participant	Signature of participant	Date	Time
Printed name of the person conducting the consent process	Signature	Date	Time