Official Title: IRON REDUCTION BY PHLEBOTOMY FOR THE TREATMENT OF DIABETES AND NONALCOHOLIC FATTY LIVER DISEASE

NCT03696797

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Wake Forest®
School of Medicine

Department/Section of *Endocrinology & Metabolism*

IRON REDUCTION BY PHLEBOTOMY TO IMPROVE DIABETES CONTROL

Informed Consent Form to Participate in Research
Donald McClain, M.D., Principal Investigator

Summary

You are invited to participate in a research study. The purpose of this research is to test a simple and safe adjunct therapy, iron reduction through blood donation, for the prevention and management of prediabetes, type 2 diabetes mellitus (T2DM) and other complications of Metabolic Syndrome (MetS) which is a group of risk factors that may increase your chances of acquiring heart disease, diabetes or stoke including nonalcoholic steatohepatitis (NASH) or fatty liver.

You are invited to be in this study because you have prediabetes or you are Type 2 on metformin or any other medications to control your diabetes, insulin and other than sulfonylureas are will exclude you from this study. Your participation in this research will involve 7- 10 visits and last about 18 months.

Participation in this study will involve blood draws each visit, you will have phlebotomy procedures, wear a glucose monitor on 3 occasions and have the option of participating in 1 or 2 sub studies that are looking at liver thickness and glucose mechanisms. All research studies involve some risks. A risk to this study that you should be aware of are:

- Any procedure that involves drawing your blood, putting needles in your veins, might cause you to feel faint or even pass out with a fainting spell, which doctors call a "vasovagal reaction". These episodes could occur on either visit, and are generally harmless as long as you do not fall.
- You may experience discomfort, bruising and/or bleeding where the needle is inserted. Occasionally some people become dizzy, lightheaded or feel faint. Infection may occur on rare occasions.
- Phlebotomy risk:
    - If you have a tendency to faint when you see blood, please tell the study nurses or investigators so that extra precautions can be taken. The risk of fainting after blood donation at the Red Cross is less than 1%, and we will monitor your blood pressure to lessen that chance further.
- "Risks and side effects related to the glucose tolerance tests include" which is part of the substudy:
    - Pain or discomfort from insertion of needles in your veins (intravenous needles) and infusion of glucose
    - May experience low blood sugars
- Risks and side effects related to the liver sub study may include:

  - There is a small chance of bruising from the Fibroscan liver ultrasound.
  - The MRI test is done in while you are laying in a tube and some people may feel claustrophobia.
- The remainder of this form contains a more complete description of this study. Please read this description carefully. You can ask any questions if you need help deciding whether to join the study. The person in charge of this study is Dr. Donald McClain. If you have questions, suggestions, or concerns regarding this study or you want to withdraw from the study his contact information: Dr. Donald McClain at [redacted]

- If you have any questions, suggestions or concerns about your rights as a volunteer in this research, contact the Institutional Review Board at [redacted] or the Research Subject Advocate at Wake Forest at [redacted].

INTRODUCTION

What are some general things you should know about research studies?
You are being invited 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. Ask us if there is anything that is not clear or if you would like more information. Take time to decide whether or not you wish to volunteer to take part in this research study. You may refuse to join, or you may withdraw your consent to be in the study for any reason, without penalty.

Research studies are designed to obtain new knowledge. This new information may help people in the future. You may not receive any direct benefit from being in the research study. There also may be risk to being in research studies.

Details about this study are discussed below. It is important that you understand this information so that you can make an informed choice about being in this research study. You will be given a copy of this consent form. You should ask the researchers named above, or staff members who may assist them, any questions you have about this study at any time.

WHY IS THIS STUDY BEING DONE?

What is the purpose of this study?
This is a treatment study to determine if reducing your body's iron stores by blood donation will improve your diabetes control and other problems associated with diabetes such as fatty liver disease. The investigators for this study have worked extensively with patients with iron overload and those with Type 2 Diabetes. The central causes of Type 2 (Adult) Diabetes remain unknown. Excess iron in the body has been shown to cause Type 2 Diabetes in individuals with certain forms of iron overload. Recent laboratory work has demonstrated significant effects of iron on glucose (sugar) metabolism, fat metabolism, and weight maintenance. Our results suggest that iron is also an important normal regulator of metabolism.

There is evidence in both iron overload and common Type 2 Diabetes that aspects of these

diseases can be reversed by reducing iron levels through phlebotomy (donating blood). Based on all of these findings, we propose that high iron triggers a number of events in different tissues, some of which will predispose to diabetes. We will therefore study normal individuals who have higher than average iron levels in tissues. We will test your glucose control through standard blood tests like the hemoglobin A1c (HgA1c is a blood test that measures your average blood sugar levels over the past 3 months) by placing a continuous glucose monitor (CGM) before and after you have donated blood to determine if decreasing your iron levels had any effect.

HOW MANY PEOPLE WILL TAKE PART IN THE STUDY?

Two hundred forty people at 2 research sites will take part in this study, including approximately 120 people at this research site. In order to identify the 120 subjects needed at Wake Forest Baptist Medical Center, we may need to screen as many as 300 as some people will not qualify to be included in the study.

There will be two optional sub studies that will be conducted only at Wake Forest Baptist Medical Center. One will look more closely at liver complications of diabetes and the other will explore whether improvements in glucose levels are due to more insulin production or improved insulin action.

Iron may also play a role in the progression of fatty liver to scarring and cirrhosis. Since 75% of people with diabetes have some degree of fatty liver, we would also like to study how your liver reacts to the lowering of iron. This Will Require some additional test, namely an MRI and a liver Ultrasound ("Fibroscan"). There will be approximately 40 people recruited at Wake Forest Baptist Medical Center for the liver sub study.

The glucose tolerance mechanisms substudy will look at the mechanism that your body uses to regulate blood sugar levels by insulin. This Will Require the frequently sample intravenous glucose tolerance test (FSIVGTT). There will be approximately 48 people recruited at Wake Forest Baptist Medical Center.

Who can participate?
Individuals age 40-75 who have been diagnosed with Type 2 Diabetes or Prediabetes for at least 3 months are eligible if their hemoglobin A1c (a measure of average blood sugar) is between 5.7-6.4% for subjects with prediabetes, undiagnosed on no medications HgbA1c 6.5 – 6.9 and 7-8.5% for subjects with type 2 diabetes and if the serum ferritin (an index of iron stores) is in the upper half of the normal range done within 1 year at the time of the screening visit. Ferritin levels for women > 50 ng/ml and for men >100 ng/ml. Additionally, participants must be on a stable lifestyle therapy program and can be taking up to 2 diabetes drugs though no sulfonylureas (e.g., glipizide, glimepiride, glyburide), glinides (repaglinide or nateglinide), or insulin are allowed. Likewise, you must not have significant anemia in order to participate.

Women who can still bear children will not be accepted into this study unless they are on an effective program of birth control. Reliable methods of birth control are: abstinence (not having sex), oral contraceptives, intrauterine device (IUD), Depo-Provera, tubal ligation. An acceptable, although less reliable method involves the careful use of condoms and spermicidal foam or gel

and/or a cervical cap or sponge. We encourage you to discuss this issue further with your physician if you have any questions.

How long will your participate in this study last?
You will be in the study for about 18 months. This requires 6-8 study visits, depending on how many phlebotomy visits are required to reach serum ferritin values in the lower range of normal (20-40 ng/mL for females and 20-40 ng/mL for males).

What will happen if you take part in the study?
You will be asked to come to the Clinical Research Unit (CRU) where studies take place at WFBMC for your study visits. Visits will occur as follows:

WHAT IS INVOLVED IN THE STUDY?

STUDY PROCEDURES: BASIC STUDY

Screening Visit (Not Fasting) – 1 hour.

You will be asked to come to the CRU in the morning.. You can take all of your normal medications as usual with water. At this visit we will review the inclusion and exclusion criteria for participation in this study and will obtain consent. You will be asked to review this form and ask any questions that you may have. You will have to sign the form before any study procedures can take place.

We will draw approximately 2 teaspoons of blood to check your serum ferritin, complete blood count (CBC) platelet, no differential, C-Reactive Protein (CRP) and Hemoglobin A1c (HbA1c), if not available through your chart within the last three months. You will be offered counseling if you are overweight as one of our standard of care counseling protocols used in the Diabetes Prevention Program.

Visit 1 (Not Fasting) – 30 minutes to 1 hour:
You will be asked to come to the Clinical Research Unit (CRU), where research studies take place at Wake Forest Baptist Medical Center (WFBMC) in the morning. At this visit, we will place on you a continuous glucose monitor (CGM). This study will use the Abbott FreeStyle Libre 14 day CGM sensor. The sensor is worn on the back of the upper arm. The sensor uses a thin, flexible filament inserted just under the skin to measure glucose every 15 minutes for the next 14 days. Once you become comfortable with the placement of the CGM you will be able to leave, you will need to bring the CGM to your next visit.

Visit 2 (Fasting) -7-14 days after Visit 1: 1-2 hours.:
You will be asked to come to the Clinical Research Unit (CRU) in the morning. We ask that you come without eating or drinking after 10 PM the previous evening. YOU MAY DRINK UNFLAVORED, UNCARBONATED WATER PRIOR TO YOUR VISIT. We encourage you to drink two liters of water the day before your visit, and an additional 16 oz. of water the morning of your visit. .You can take all of your normal medications as usual with water. During this visit a complete medical history will be obtained, , and approximately 2 teaspoons of blood

will be drawn for a complete metabolic panel (CMP), ferritin , lipid panel, liver and kidney function tests, , and insulin levels. We will measure your height, weight and abdominal girth (measurement of the distance around your abdomen at the level of your belly button). You will have an Ultrasound Fibroscan (WFBH site only), the Fibroscan is a noninvasive imaging study that evaluates the degree of liver stiffness, which is a measure of the scarring or fibrosis that can occur with diabetes or fatty liver. It does this by determining the speed of sound waves through the liver utilizing a sonogram.

During this visit, you will return the glucose monitor and you will undergo randomization. Randomization involves comparing different treatments. In many research studies, one group of participants will get one treatment and another group will get a different treatment. In a randomized study, participants are put in one group or the other by random chance. This means that a computer will decide by chance which group a participant is in, not the doctors running the study. In this study, you have a 1:1 chance of either being in the treatment group or in the control group. We would like for all the participants involved to not know what group they are in. So both groups will have an IV or needle stuck into a vein in the arm. Prior to starting the phlebotomy procedure, we will measure your blood count, to be sure you are not anemic, and your blood pressure, to be sure you are not dehydrated.

TREATMENT GROUP- if you are randomized to this group, you will have a Unit of blood (~500ml, or about two cups, the same amount you would donate at the Red Cross).

CONTROL GROUP- if you are randomized to this group will not donate blood, but will have a needle inserted into a vein in your arm.

Subjects in either group will not know to which they have been assigned, all subjects will have a sleep mask (like a blindfold, covering the eyes, held on with an elastic band) or a towel will be used as a barrier and will be placed between all subjects and the phlebotomy bag so the subject will not know whether blood was actually drawn.. All subjects will be offered a zero-caloric drink and a small snack towards the end of the visit. Your blood pressure will again be monitored at the end of the visit.

We ask that you maintain your lifestyle as is and make no drastic changes to diet or maintenance of your diabetes, unless otherwise indicated by your regular Doctor. We will track your progress through your medical charts. We will check your Iron levels and Hemoglobin to be sure that you do not become anemic.

Visits 3-6 (Not Fasting) – occurring at 8 week intervals following Visit 2; 1-2 hours.
You will be asked to come to the Clinical Research Unit (CRU) in the morning, you can take all of your normal medications as usual with water. These visits will occur at 8-week intervals, with visit 3 occurring ~8 weeks after visit 2, and will serve as follow-up phlebotomy visits for all subjects. You will return for a review of your progress and blood donation (phlebotomy). We will continue phlebotomy visits on this schedule until your iron levels are at the target (in the lower third of the normal range). This will typically take three to four visits total. We draw approximately ¼ teaspoon of blood to measure your hemoglobin prior to phlebotomy, to be sure that you do not become anemic, and your serum ferritin levels (iron) at each visit.

Once your serum ferritin levels are in the target range, you will no longer come in for phlebotomy visits and will instead be scheduled for the end of study (EOS) sequence.

End of Study Visit 1 (Fasting) – 6 months ± 2 weeks after LAST phlebotomy visit; ~1 hour. You will be asked to come to the CRU in the morning. We ask that you come without eating or drinking after 10 PM the previous evening. YOU MAY DRINK UNFLAVORED, UNCARBONATED WATER PRIOR TO YOUR VISIT. We encourage you to drink two liters of water the day before your visit, and an additional 16 oz. of water the morning of your visit. You can take all of your normal medications as usual with water. At this visit we will review your progress and measure your weight, blood pressure, we will draw approximately 2 teaspoons of blood to test your c-reactive protein, CMP, CBC platelet no differential,, insulin, Hemoglobin Alc, lipid panel,, and ferritin levels (iron), the Fibroscan will be at the (WFBH site only). We will also place on you an Abbott Libre continuous glucose monitor (CGM) which you will return by mail 14 days after placement as your next visit will not occur for 6 months.

End of Study Visit 2 (Fasting) – 6 months ± 2 weeks after EOS Visit 1; ~1 hour. You will be asked to come to the CRU in the morning. We ask that you come without eating or drinking after 10 PM the previous evening. YOU MAY DRINK UNFLAVORED, UNCARBONATED WATER PRIOR TO YOUR VISIT. We encourage you to drink two liters of water the day before your visit, and an additional 16 oz. of water the morning of your visit. You can take all of your normal medications as usual with water. At this visit we will review your progress and measure your weight, blood pressure, we will draw approximately 2 teaspoons of blood to test your c-reactive protein, CBC platelet no differential, CMP, , insulin, hemoglobin A1c, lipid panel, and ferritin levels (iron), the Fibroscan will be at the (WFBH site only). We will also place on you an Abbott Libre continuous glucose monitor (CGM), which you will return by mail 14 days after placement.

Main Study Calendar:

	Screening (Not fasting)	Visit 1 (Not Fasting)	Visit 2 (fasting)	Visit 3 (Not Fasting)	Visit 4 (Not Fasting)	Visit 5 (Not Fasting	Visit 6 (Not Fasting)	EOS 1 (fasting)	EOS 2 (fasting)
Consent	X								
Inclusion/Exclusion	X								
Medical History	X								
Review Medications	X		X	X	X	X	X	X	
Vital Signs (following BP protocol)	X		X	X	X	X	X	X	X
Physical Exam	X							X	X
Adverse Events	X		X	X	X	X	X	X	X
CGM Placement		X						X (returned by mail)	X (returned by mail)
Return CGM and Download Data			X						
Hemoglobin WFU-CRU	X		X	X	X	X	X	X	X
Ferritin, serum	X (if not available)		X	X	X	X	X	X	X
HgbA1c	X (if not available)							X	X
CMP (14)			X					X	X
CBC Platelet no	X							X	X

Differential									
CRP	X							X	X
Insulin (fasting)			X					X	X
Lipid panel (fasting)			X					X	X
Fibroscan			*X					*X	*X
Blood for Research Storage (to be sent to Wake Forest)	X		X	X	X	X	X	X	X
Phlebotomy Procedure (including all vital sign measurements prior and post procedure)			X	X	X	X	X		
Discarded Phlebotomy sample will be sent to the Olin Physical Lab-WFBH site only			X	X	X	X	X		

P CGM Device Placement
*X Fibroscan – WFBH site only

WHAT IS INVOLVED IN THE LIVER SUBSTUDY?

STUDY PROCEDURES: LIVER SUBSTUDY

The Screening Visit and Visit 1 will be the same as the Basic Study

Visit 2 Liver Substudy – 1 hour
In addition to the other studies planned Visit 2 of the Basic Study, those in the Liver Substudy will have: Magnetic Resonance Imaging (MRI), FIBROSCAN done at Visit 2.

Both Control and Treatment Groups will have an Ultrasound Fibroscan, the Fibroscan is a noninvasive imaging study that evaluates the degree of liver stiffness, which is a measure of the scaring or fibrosis that can occur with diabetes or fatty liver. It does this by determining the speed of sound waves through the liver utilizing a sonogram. The Magnetic Resonance Imaging (MRI) is a test that uses powerful magnets, and a computer to make detailed pictures inside your body. Neither test uses radiation.

A radiologist will interpret the MRI scans and if any silent hepatic lesions are detected or other abnormalities we will inform you and, if you desire your physician.

Following Visit 2, the RANDOMIZATION, PHLEBOTOMY, and END OF STUDY (E.O.S.) visits will occur just as in the Basic Study, the End of Study 1 will repeat the Fibroscan and End of Study 2 will repeat the Fibroscan and MRI.

Liver Substudy Calendar:

Procedure	Screening Visit	Month 0		Months 2-8 (as needed)			Month 11-12	Month 17-18
		Visit 1	Visit 2	Visit 3	Visit 4	Visit 5, 6, ect.	E.O.S. 1	E.O.S. 2
*Fibroscan			X				*X	*X
*MRI			**X					**X

*X – Fibroscan (additional test for Liver substudy) WFBH site only
** - MRI

Please initial ____Yes I am interested in the liver substudy ___No I am not interested

WHAT IS INVOLVED IN THE GLUCOSE TOLERANCE MECHANISM SUBSTUDY?

STUDY PROCEDURES: GLUCOSE TOLERANCE MECHANISM SUB STUDY

The Screening Visit and Visit 1 will be the same as the Basic Study.

Visit 2 Glucose Tolerance Mechanism Substudy – 3-4 hours
Both Control and Treatment Groups will have a glucose test that uses an IV it is called a Frequent Sample Intravenous Glucose Tolerance Test (FSIVGTT). There will be a plastic catheter (IV) placed in a vein in your arm and blood samples will be taken. A second IV will be placed in your other arm and dextrose (sugar water) will be given through that IV. For this test you will be given 300mg/kg (or an average total of 20 grams) of glucose IV over one minute with bloods for insulin and glucose determination collected at one minute intervals for 6 minutes, then at two minute intervals until 18 minutes. At 20 minutes, you will be given 0.04 Unites/kg og regular insulin, or an average of 2-3 Units total. Samples of blood will continue to be taken until a total of 180 minutes have elapsed. This amount of insulin is much less, than your own body will be making in response to the glucose we gave you.

During this visit, the total amount of blood taken from you will be approximately ¾ cup (10 tablespoons). When your tests are completed, you will be given a snack and meal voucher.

Following Visit 2, the RANDOMIZATION, Phlebotomy, and END OF STUDY (E.O.S.) visits will occur just as in the Basic Study, with the addition of the FSIVGTT at E.O.S 1 and E.O.S. 2.

Glucose Tolerance Mechanism Substudy Calendar:

Procedure	Screening Visit	Month 0		Months 2-8 (as needed)			Month 11- 12	Month 17- 18
		Visit 1	Visit 2	Visit 3	Visit 4	Visit 5, 6, ect.	E.O.S. 1	E.O.S. 2
FSIVGTT			**X				**X	**X
Fibroscan			*X				*X	*X

**X – Frequent Sample Intravenous Glucose Tolerance Test (FSIVGTT)
*-Fibroscan WFBH site only

Please initial ____Yes I am interested in the Glucose Tolerance Mechanism substudy
___ No I am not interested in the Glucose Tolerance Mechanism substudy

Do you request that we send important medical findings from your study tests/exams to your personal physician?

[ ] Yes [ ] No _____ Initials

Storage of Biological Tissue

In order to participate in this study, you must be willing to provide this sample for future research. These samples will be kept and may be used in future research to learn more about other diseases. Your samples will be obtained in the Clinical Research Unit (CRU) at Wake Forest University Baptist Medical Center or UNC. The sample will be stored in Dr. Donald McClain's research lab located at the Center on Diabetes, Obesity and Metabolism at BioTech 3 West 030 of the Wake Forest Baptist Medical Center and it will be given only to researchers approved by Dr. McClain. An Institutional Review Board (IRB) must also approve any future research study using your blood sample.

WFBH participants only:
The discarded phlebotomy blood will be de-identified and will be picked up by a representative from the Dr. Kim-Shapiro Lab, the sample will be stored in the Olin Physical Lab on the Reynolda campus, room 216. The blood will be used for in vitro experiments aiming to prevent thrombosis in extracorporeal circulation devices. An Institutional Review Board (IRB) must also approve any future research study using your blood sample.

Your blood samples will be stored with a unique identifier and will not include any identifiable information about you such as your name, address, telephone number, social security number, medical record number or any of the identifiers outlined in the HIPAA Privacy Rule. The unique identifier will be a randomly assigned number and only the principal investigator will have access to the code that links the unique identifier to you. Your name, address, social security number, etc., will never be disclosed to future researchers and neither will the code that links your identifiers to the sample.

How Long Will I Be in the Study?

You will be in the study for about 18 months. This requires 6-8 study visits, depending on how many units of blood are donated.

What Are the Risks of the Basic Study?

Being in this study involves some risk to you. You should discuss the risk of being in this study with the study staff. Basic study risks include those related to "Risks and side effects related to the glucose tolerance tests include" which is part of the substudy:

- Pain or discomfort from insertion of needles in your veins (intravenous needles) and infusion of glucose
- Any procedure that involves drawing your blood, putting needles in your veins, might cause you to feel faint or even pass out with a fainting spell, which doctors call a "vasovagal reaction". These episodes could occur on either visit, and are generally harmless as long as you do not fall.
- If you have a tendency to faint when you see blood, please tell the study nurses or investigators so that extra precautions can be taken. The risk of fainting after blood donation at the Red Cross is less than 1%, and we will monitor your blood pressure to lessen that chance further.
- You may experience discomfort, bruising and/or bleeding where the needle is inserted. Occasionally some people become dizzy, lightheaded or feel faint. Infection may occur

on rare occasions.

WHAT ARE THE ADDITIONAL RISKS OF THE LIVER SUBSTUDY?

There is a small chance of bruising from the Fibroscan liver ultrasound. The MRI test is done in while you are laying in a tube and some people may feel claustrophobia.

WHAT ARE THE ADDITIONAL RISKS OF THE GLUCOSE MECHANISMS SUBSTUDY?

A small amount of insulin is injected during the FSIVGTT test, and this can cause your blood sugar to go too low (hypoglycemia). This can be corrected easily with oral or i.v. glucose.

UNUSUAL AND RARE SIDE EFFECTS

- Inserting needles in your veins can introduce a risk of infection. Should you note any signs of an infection (redness, inflammation, swelling or severe pain in the site, or fever), you should call the investigators immediately so that they can examine the intravenous site.

In addition, there is a slight risk of a breach of confidentiality. We will do our best to protect your confidential information. There also may be other side effects that we cannot predict. You should tell the research staff about all the medications, vitamins and supplements you take and any medical conditions you have. This may help avoid side effects, interactions and other risks.

WOMEN WHO CAN STILL BEAR CHILDREN OR WHO MIGHT BE PREGNANT WILL NOT BE ACCEPTED INTO THIS STUDY UNLESS THEY ARE ON AN ACCEPTABLE METHOD OF BIRTH CONTROL

ARE THERE BENEFITS TO TAKING PART IN THE STUDY?

You may or may not receive benefit from participating in the study. You will find out your glucose tolerance information and if you are at high risk for developing diabetes. The information we get from this study may help us better to treat you and future patients with iron overload.

WHAT OTHER CHOICES ARE THERE?

You may choose not to participate in this study. You should continue to receive the usual care for your diabetes from your normal healthcare provider; there are multiple medications for diabetes, and this study is not designed to replace those. Your iron levels are not at a level such that usual medical care would want to change them although by donating blood at the Red Cross or eating less red meat could decrease your iron.

WHAT ABOUT MY HEALTH INFORMATION?

In this research study, any new information we collect from you and/or information we get from your medical records or other facilities about your health or behaviors is considered Protected Health Information. The information we will collect for this research study includes**:**

- Name
- Address
- Telephone number
- Social Security Number
- Family medical history
- Allergies
- Current and past medications or therapies
- Information from a physical examination, such as blood pressure reading, heart rate, breathing rate, and temperature
- Information from the glucose tolerance tests, calorimetry, ultrasound and MRI scans performed as part of the study

The social security number will be collected for the purposes of compensation and IRS reporting.

If this research study involves the diagnosis or treatment of a medical condition, then Protected Health Information collected from you during this study will be placed in your medical record, and may be used to help treat you, arrange payment for your care, or assist with Medical Center operations.

We will make every effort to keep your Protected Health Information private. We will store records of your Protected Health Information in a cabinet in a locked office or on a password protected computer. Only the following people or organizations will be granted access to your Protected Health Information:

1) The study investigator and his/her staff, or others at Wake Forest University Health Sciences or UNC Chapel Hill who oversee research

2) Other people or laboratories providing services for this research project on behalf of Wake Forest University Health Sciences, Wake Forest University Baptist Medical Center, or UNC Chapel Hill

3) Others who will have access to your information for this research project are the University's and VA's Institutional Review Board (the committee that oversees research studying people) and authorized members of the University's workforce who need the information to perform their duties (for example: to provide treatment, to ensure integrity of the research, and for accounting or billing matters).

4) Monitors, auditors, IRB or other regulatory agencies will be granted direct access to the participant's original medical record for verification of clinical trial procedures or data, without violating confidentiality of the participant and to the extent permitted by other applicable laws.

5) In conducting this study, we may share your information with a group outside the VA, WFBMC or UNC Chapel Hill. The information we share may include information that

directly identifies you. That group is the National Institute of Health, a federal agency that needs to confirm the accuracy of the results submitted to the government.

6) A Data Safety and Monitoring Committee, an independent group of experts, will be reviewing the data from this research throughout the study.

If required by law or court order, we might also have to share your Protected Health Information with a judge, law enforcement officer, government agencies, or others. If your Protected Health Information is shared with any of these groups it may no longer be protected by federal or state privacy rules.

Any Protected Health Information collected from you in this study that is maintained in the research records will be kept for an indeterminate period of time. This authorization does not expire. Any research information entered into your medical record will be kept for as long as your medical record is kept by the Medical Center. You will not be able to obtain a copy of your Protected Health Information in the research records until all activities in the study are completely finished.

You can tell Dr. Donald McClain that you want to take away your permission to use and share your Protected Health Information at any time by sending a letter to this address:

Donald McClain, M.D.
Wake Forest School of Medicine
Section of Endocrinology & Metabolism
[redacted]

However, if you take away permission to use your Protected Health Information you will not be able to be in the study any longer. We will stop collecting any more information about you, but any information we have already collected can still be used for the purposes of the research study.

By signing this form you give us permission to use your Protected Health Information for this study.

If you choose to participate in this study, your medical record at Wake Forest University Baptist Medical Center or UNC Chapel Hill will indicate that you are enrolled in a clinical trial. Information about the research and any medications or devices you are being given as a participant may also be included in your medical record. This part of the medical record will only be available to people who have authorized access to your medical record. If you are not a patient at this Medical Center, a medical record will be created for you anyway to ensure that this important information is available to doctors in case of an emergency.

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 Web site at any time.

Laboratory test results and other medical reports created as a result of your participation in the research study may be entered into the computer systems of Wake Forest University Health Sciences, North Carolina Baptist Hospital and UNC Chapel Hill. These will be kept secure, with access to this information limited to individuals with proper authority, but who may not be directly involved with this research study.

A North Carolina Baptist Hospital (NCBH) medical record will be created for all study participants. Information about your participation in the study will be placed in the NCBH medical record, along with any routine medical test results that were obtained at NCBH as part of this study.

Will Your Research Records Be Confidential?

This research is covered by a Certificate of Confidentiality from the National Institutes of Health. The researchers with this Certificate may not disclose or use information, documents, or biospecimens that may identify you in any federal, state, or local civil, criminal, administrative, legislative, or other action, suit, or proceeding, or be used as evidence, for example, if there is a court subpoena, unless you have consented for this use. Information, documents, or biospecimens protected by this Certificate cannot be disclosed to anyone else who is not connected with the research except, if there is a federal, state, or local law that requires disclosure (such as to report child abuse or communicable diseases but not for federal, state, or local civil, criminal, administrative, legislative, or other proceedings, see below); if you have consented to the disclosure, including for your medical treatment; or if it is used for other scientific research, as allowed by federal regulations protecting research subjects.

WHAT ARE THE COSTS?

There are no costs to you for taking part in this study. All study costs, including any study visits and procedures related directly to the study, will be paid for by the study. Costs for your regular medical care, which are not related to this study, will be your own responsibility.

WILL YOU BE PAID FOR PARTICIPATING?

You will be financial compensated for your involvement in this study to help defray costs of time and transportation. You will be paid $100.00 upon successful completion of the screening visit. You will be paid $50.00 after completing Visit 1 (CGM placement visit) and $50.00 per completed phlebotomy visits. You will be paid $100.00 per visit after completing End of Study Visit 1 and End of study Visit 2. Your reimbursement will likely total $400 -$600 if you successfully complete ALL study-related visits..
If you withdraw from the study before finishing the treatment, you will not be paid for visits not completed.

If you participate in the Liver Substudy you will be compensated an additional $50.00 for each MRI you complete. If you participate in the Glucose Tolerance Mechanism Substudy you will be compensated an additional $200.00 and will be given $10.00 for your meal with each FSIVGTT that you complete.

To receive payment, you must provide your social security number, name and address so that we can comply with IRS (Internal Revenue Service) reporting requirements. When payments are reported to the IRS we do not let them know what the payment is for, only that you have been paid. If you do not wish to provide this information you can still take part in this study but you will not be paid.

WHO IS SPONSORING THIS STUDY?

This study is being sponsored by funds from the National Institutes of Health. The researchers do not hold a direct financial interest in the study.

WHAT HAPPENS IF YOU EXPERIENCE AN INJURY OR ILLNESS AS A RESULT OF PARTICIPATING IN THIS STUDY?

Should you experience a physical injury or illness as a direct result of your participation in this study, Wake Forest University School of Medicine maintains limited research insurance coverage for the usual and customary medical fees for reasonable and necessary treatment of such injuries or illnesses. To the extent research insurance coverage is available under this policy the reasonable costs of these necessary medical services will be paid, up to a maximum of $25,000. Wake Forest University Baptist Medical Center holds the insurance policy for this coverage. It provides a maximum of $25,000 coverage for each claim and is limited to a total of $250,000 for all claims in any one year. The Wake Forest University School of Medicine, and the North Carolina Baptist Hospitals, Incorporated do not assume responsibility to pay for these medical services or to provide any other compensation for such injury or illness. Additional information may be obtained from the Medical Center's Director of Risk and Insurance Management, at [redacted].

If you are injured, the insurer may require information such as your name, social security number, and date of birth in order to pay for your care. This is because the insurer is required by law to report any payments made to cover the care of any persons who are members of a government insurance plan to the Department of Health and Human Services.

You do not give up any legal rights as a research participant by signing this consent form. For more information on medical treatment for research related injuries or to report a study related illness, adverse event, or injury you should call Dr. Donald McClain at [redacted] or after hours at [redacted].

WHAT ARE MY RIGHTS AS A RESEARCH STUDY PARTICIPANT?

Taking part in this study is voluntary. You may choose not to take part or you may leave the study at any time. Refusing to participate or leaving the study will not result in any penalty or loss of benefits to which you are entitled. If you decide to stop participating in the study we encourage you to talk to the investigators or study staff first to learn about any potential health or safety consequences. The investigators also have the right to stop your participation in the study at any time. The physician may choose to stop any part of the study before it is finished if it

becomes medically necessary to do so. If the investigator feels that participation in this study would delay other needed medical therapy for any conditions either related or unrelated to the underlying reasons for this study, you would be removed from the study so that treatment could begin.

You will be given any new information we become aware of that would affect your willingness to continue to participate in the study.

WHOM DO I CALL IF I HAVE QUESTIONS OR PROBLEMS?

For questions about the study or in the event of a research-related injury, contact the study investigator, Dr. Donald McClain at [redacted] or after hours at [redacted].

The Institutional Review Board (IRB) is a group of people who review the research to protect your rights. If you have a question about your rights as a research participant, or you would like to discuss problems or concerns, have questions or want to offer input, or you want to obtain additional information, you should contact the Chairman of the IRB at [redacted].

You will be given a copy of this signed consent form.

SIGNATURES

I agree to take part in this study. I authorize the use and disclosure of my health information as described in this consent and authorization form. If I have not already received a copy of the Privacy Notice, I may request one or one will be made available to me. I have had a chance to ask questions about being in this study and have those questions answered. By signing this consent and authorization form, I am not releasing or agreeing to release the investigator, the sponsor, the institution or its agents from liability for negligence.

Subject Name (Printed):_____

Subject Signature: _____ Date: _____Time:_____ am pm

Person Obtaining Consent:_____ Date:_____ Time:_____ am pm