Wake Forest™
School of Medicine

Department of Neurology

INTRANASAL INSULIN AND POST-STROKE COGNITION

Informed Consent Form to Participate in Research

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INTRODUCTION

You are invited to be in a research study. Research studies are designed to gain scientific knowledge that may help other people in the future. You are being asked to take part in this study because you have recently had an ischemic stroke or an Intracerebral Hemorrhage (ICH). An ischemic stroke is a type of stroke in which a blood vessel becomes blocked and prevents blood flow to part of the brain. An Intracerebral hemorrhage (ICH) is a type of stroke in which blood suddenly bursts into brain tissue, causing damage to the brain. Your participation is voluntary. Please take your time in making your decision as to whether or not you wish to participate. Ask your study doctor or the study staff to explain any words or information contained in this informed consent document that you do not understand. You may also discuss the study with your friends and family.

WHY IS THIS STUDY BEING DONE?

The purpose of this research study is to determine whether participants who have had a stroke and receive insulin as a nasal spray into the nasal passages have improved cognition, (ability to think and remember,) and to measure differences in burden among the participant caregivers. Post-stroke cognitive decline is a public health problem. Overall, almost two-thirds of stroke survivors have cognitive decline that we see in memory, language, and judgment problems. This cognitive decline impairs survivors' return to work and social function, and reduces life satisfaction and ability to return to normal living, even after a mild stroke. These changes directly affect their activities of daily living. As a result, it is also a major strain on caregivers. We will also look at the impact of intranasal insulin on markers of inflammation in the blood. Insulin is approved by the US Food and Drug Administration (FDA). However, it has not been approved for use in this manner for patients who have had stroke, and we do not know if it will be effective to help improve your cognition.

In this study intranasal insulin will be compared to placebo. A placebo is a substance, like a sugar pill, that is not thought to have any effect on your disease or condition. In this study you will either receive the active study medication, intranasal insulin, or intranasal saline, which is the non-active placebo. Placebos are used in research studies to see if the drug being studied

really does have an effect.

HOW MANY PEOPLE WILL TAKE PART IN THE STUDY?

There will be 20 people at Wake Forest Baptist Medical Center taking part in this study.

WHAT IS INVOLVED IN THE STUDY?

You will undergo baseline cognitive testing 6 weeks – 6 months after your stroke and you will be randomized into one of the study groups described below. Randomization means that you are put into a group by chance. It is like flipping a coin. You will have an equal chance of being placed in the intranasal insulin 20 IU twice/day or the intranasal saline twice/day group. Neither you nor the investigator will know which study drug you are receiving. This is done so that a fair evaluation of results can be made. This information is available to the researchers if needed in an emergency.

If you take part in this study, you will have the following visits which will include the listed tests and procedures:

Consenting Process:

If you are found eligible and you agree, you will be signing this consent form, randomized into the study, and you will be scheduled for the Baseline Visit. Your caregiver will also sign this consent form, accompany you to your study visits, and complete a questionnaire at each visit.

Baseline Visit 1:

- Demographic and history data collection
- Fasting blood draw (You will need to fast, or not consume any food or drink [except water], for 12 hours before blood draw); the blood draws will be at the beginning of the visit after which we will give you a snack prior to cognitive testing.
- Cognitive testing (evaluation of your thinking and memory); you will be asked to do several tasks, such as remembering stories, and listing words and designs. These are not intelligence tests, and we will not be determining your "IQ". These tests will take about an hour to complete. You may choose not to answer any questions or items in any test.
- Activity and feeling questionnaires
- Stroke assessments
- Caregiver questionnaire
- Begin three-week study drug treatment (intranasal insulin 20 IU twice/day or intranasal saline twice/day; plus blood glucose testing twice/day, on three days of eachweek) with follow-up phone calls at end of first and second week to ensure proper administration and assess for early undesired effects)

Visit 2: End of Treatment Visit (approximately 3 weeks after Visit 1)

- End of study drug treatment and blood glucose measurements; Return intranasal container and glucometer
- Repeat the above baseline visit procedures:

- Fasting blood draw (12 hour fasting before blood draw); the blood draws will be at the beginning of the visit after which we will give you a snack prior to cognitive testing.
- Cognitive testing (evaluation of your thinking and memory); you will be asked to do several tasks, such as remembering stories, and listing words and designs. These are not intelligence tests, and we will not be determining your "IQ". These tests will take about an hour to complete. You may choose not to answer any questions or items in any test.
- Activity and feeling questionnaires
- Stroke assessments
- Caregiver questionnaire

- **Visit 3: Study End (approximately three weeks after Visit 2)**
- Cognitive testing
- Feeling questionnaire
- Caregiver questionnaire

After completion of the baseline visit, you will administer the intranasal insulin study drug twice a day for 3 weeks. The study insulin is administered using a Vianase® device. This small, reusable device (about the size of two decks of cards) is operated on a rechargeable battery or plugged into an electrical outlet. The device has a plastic delivery piece that is placed against the openings of the nose. The specified dose of study drug is added to the device each time it is used. To use the device, you will breathe in through your nose and out through your mouth until the dose of study drug is administered (for 20 seconds). You will use the device in each nostril. You will additionally check your blood glucose level twice a day, three days a week, for three weeks. Blood glucose is monitored with a glucometer. You will insert a blood glucose strip into the device, prick your finger, and draw the blood into the strip to obtain a reading. Both you and your caregiver will be trained to use the delivery device and glucometer.

It is important that you tell the study team about any other medications that you are taking before and during the study or if there are any changes to your medications. While you are taking the study drug you should not take medications that are prohibited. Your study doctor will discuss the medications that are prohibited with you and your caregiver.

As part of the baseline visit 1 and visit 2, a blood sample will be obtained and DNA from your blood sample will be purified. DNA, or deoxyribonucleic acid, stores and transmits inherited traits, such as eye color or blood type. As part of this research project, your DNA will be studied in an effort to find out if there are genes that contribute to medical conditions that are part of this study. Because we do not know how the results of this DNA and study relate to your individual health, the results of the research will not be given to you or your doctor without your permission. The results will also not be placed in your medical records.

Storage of Biological Tissue

If you agree to participate in this study, you will have approximately 3½ teaspoons of blood withdrawn from a vein at two of the visits. The total amount of blood withdrawn during the study will be approximately 7 teaspoons or 2 tablespoons. Your blood sample will be kept and may be used in future research. Your sample will be obtained in the Clinical Research Unit at Wake Forest University Baptist Medical Center. An Institutional Review Board (IRB) must approve any future research study using your tissue sample.

Your blood sample will be frozen and stored with a unique identifier until the end of the study when it will be sent to Assaygate in Ijamsville, MD, for analysis 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.

The research that may be done with your sample is not designed to help you specifically. The results of the research done with your blood sample will not be given to you or to your doctor. These results will not be put in your medical records. The research using your blood sample will not affect your care. Your blood sample will be used only for research and will not be sold. The findings from this research may result in the future development of products that are of commercial value. There are no plans to share any of the profits with you which may occur as a result of this research.

Sometimes blood samples used for genetic research may provide information about diseases that are passed on in families. Even if your blood sample is used for this kind of research, the results will not be told to you or members of your family, and will not be put in your health records.

The choice to let your blood sample be kept for future use is up to you. No matter what you decide to do, it will not affect your care in this study. If you decide now that your blood sample can be kept for research, you can change your mind at any time. Just contact your study investigator, Cheryl Bushnell, MD at [redacted] and let her know that you do not want your blood sample used, and it will no longer be used for research. Otherwise, the blood sample may be kept until it is used up or destroyed.

In the future, people who perform research may need to know more about your health. While the study investigator may give reports about your health, he/she will NOT be given your name, address, phone number, or any other identifying information about who you are, unless you agree to be contacted in the future.

_____ Yes I do want to participate in the storage of tissue samples portion of this study

_____ NO I do not want to participate in the storage of tissue samples portion of this study

HOW LONG WILL I BE IN THE STUDY?

You will be in the study for about 2 months. You may stop participating at any time. 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.

WHAT ARE THE RISKS OF THE STUDY?

Being in this study involves some risk to you. You should discuss the risk of being in this study with the study staff.

Intranasal Insulin

No serious adverse reactions to insulin given through the nasal passages have been observed in similar studies. Insulin given in this manner has not been associated with low blood glucosein previous studies. Nevertheless, the study staff will train you to recognize signs of low blood glucose such as shaking, fast heartbeat, sweating, dizziness, anxiousness, hunger, impaired vision, weakness, headache, and irritability. If you develop any of these symptoms, eat a snack, call the study staff at [redacted] between 8am and 5pm or [redacted] after 5pm and ask for the neurologist on call. Also, call your primary provider. If you experience severe symptoms that do not improve with eating a snack, call 911. A few participants in previous studies complained of "drippy nose" after being given the study drug, but these symptoms did not persist beyond the initial use of the study drug. As with any drug, there may be unexpected side effects to nasal insulin. Although insulin has been safely administered intravenously, the potential toxicity of the proposed clinical formulation to the nasal cavity and other locally exposed tissues has not been evaluated in animal studies.

Blood Draws

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. Frequent donation of blood can result in low iron in your blood (iron deficient anemia).

Reproductive Risks

Pregnant women are excluded from participation in this study. If you are a sexually active woman of childbearing potential and have not been using a reliable method of birth control, two negative pregnancy tests performed 15 days apart are required to check for possible early pregnancy prior to starting the study drug. Reliable methods of birth control include consistent use of a birth control pill, vaginal ring, diaphragm, IUD, condom, hormone patch, or birth control implant.

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.

Taking part in this research study may involve providing information that you consider confidential or private. Efforts, such as coding research records, keeping research records secure and allowing only authorized people to have access to research records, will be made to keep your information safe.

A Data Safety Officer, an independent expert, will be reviewing the data from this research throughout the study.

ARE THERE BENEFITS TO TAKING PART IN THE STUDY?

If you agree to take part in this study, there may or may not be direct benefit to you. We hope the information learned from this study will benefit other people in the future.

WHAT OTHER CHOICES ARE THERE?

You do not have to choose to be in this study to receive treatment for post-stroke care. Other options are readily available and include rehabilitation with physical and/or occupational therapies, follow up care, and support groups. However, currently there are no treatments that improve cognitive recovery.

WHAT ABOUT MY HEALTH INFORMATION?

In this research study, any information we get from you and/or 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:

- Demographic information, for example date of birth, sex, race, years in residence, education, marital status, occupation, living situation and level of independence
- Contact and informant information
- Family history
- Stroke hospital data
- Stroke risk factors

If this research study involves the diagnosis or treatment of a medical condition, then Protected Health Information collected from you during this study may 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 School of Medicine who oversee research

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

3) American Heart Association, the sponsor

4) Federal Agencies including, but not limited to, the Food and Drug Administration (FDA) and the Office for Human Research Protection (OHRP)

5) Kurve Technology (the company that manufactures the nasal insulin device)

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 at least six years after the study is finished. At that time any research information not already in your medical record will either be destroyed or it will be de-identified. 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.

If you choose to participate in this study, your medical record at Wake Forest University Baptist Medical Center 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.

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 and North Carolina Baptist Hospital. 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 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.

You can tell Cheryl Bushnell, M.D. 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:

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.

WHAT ARE THE COSTS?

There are no costs to you for taking part in this study. All study costs, including any study medications 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 receive a $25.00 gift card, after the completion of the second study visit, if you participate in this study.

The findings from this research may result in the future development of products that are of commercial value. There are no plans to provide you with financial compensation or for you to share in any profits if this should occur.

WHO IS SPONSORING THIS STUDY?

This study is being sponsored by the American Heart Association. The sponsor is providing money or other support to Wake Forest University Health Sciences to help conduct this study. The researchers do not, however, hold a direct financial interest in the sponsor or the product being studied.

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 Cheryl Bushnell, M.D. 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. This could be because it is in your best medical interest, your condition worsened, new information becomes available, you had an unexpected reaction, failed to follow instructions, or because the entire study has been stopped
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, Cheryl Bushnell, M.D. 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.

We can send copies of your test results to your personal physician. Even if you do not wish to have any of your medical information sent to your physician, you can still participate in this research study.

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

[ ] Yes [ ] No _____ Initials

Subject Name (Printed):_____

Subject Signature: _____ Date: _____Time:_____ am pm

Person Obtaining Consent (Printed):_____

Obtaining Consent Signature: _____ Date: _____Time: _____ am pm

Legally Authorized Representative Name (Print):_____

The above named Legally Authorized Representative has legal authority to act for the research subject based upon (specify health care power of attorney, spouse, parent, etc.)

Relationship to the Subject:_____

Legal Representative Signature: _____ Date: _____Time: _____ am pm

Study Partner Information & Consent

As the participant's study partner, you have important tasks that need to be carried out in order for the study to be conducted in the safest and best manner possible. These responsibilities include:

- You must attend 3 study visits to answer a questionnaire about caregiver strain and stress.

- You may also be asked to help administer the intranasal spray and perform blood glucose testing.

If for some reason you become unable to carry out your responsibilities, please tell the study coordinator immediately. You may be asked to help find someone else close to the participant who can take over your duties.

Signatures

I have read all the preceding information which describes both the participant's responsibilities in the study and my involvement as the subject's study partner. The study has been explained to me in detail, and all my questions have been answered.

_____	_____	_____
Study Partner's Name (printed)	Signature	Date / Time

_____	_____	_____
Person Obtaining Consent (print)	Signature	Date / Time