Trial Consent Form for:
Intranasal Insulin for Improving Cognitive Function in Multiple Sclerosis (NCT02988401)
Date of Consent Form 7/17/2020

If you are using Epic for this study, fax a copy of the signed consent form to 410-367-7382.

Patient I.D. Plate

RESEARCH PARTICIPANT INFORMED CONSENT AND PRIVACY AUTHORIZATION FORM

Protocol Title: **Intranasal insulin for improving cognitive function in multiple sclerosis**

Application No.: **IRB00095554**

Sponsor: **Department of Defense**

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1. What you should know about this study:

- You are being asked to join a research study. This consent form explains the research study and your part in it. Please read it carefully and take as much time as you need. Ask your study doctor or the study team to explain any words or information that you do not understand.
- You are a volunteer. If you join the study, you can change your mind later. There will be no penalty or loss of benefits if you decide to quit the study.
- During the study, we will tell you if we learn any new information that might affect whether you wish to continue to participate.
- If we think your participation in this study may affect your clinical care, information about your study participation will be included in your medical record, which is used throughout Johns Hopkins. Doctors outside of Johns Hopkins may not have access to this information. You can ask the research team to send this information to any of your doctors.
- When Johns Hopkins is used in this consent form, it includes The Johns Hopkins University, The Johns Hopkins Hospital, Johns Hopkins Bayview Medical Center, Howard County General Hospital, Johns Hopkins Community Physicians, Suburban Hospital, Sibley Memorial Hospital and All Children's Hospital.
- Biospecimens will be collected in this study. Biospecimens may include any of the following: blood, tissue, saliva, urine, bone marrow, cells, etc. Most biospecimens contain DNA, which is the genetic code for each person.

- A description of this clinical trial will be available on http://www.ClinicalTrials.gov, as required by U.S. Law. This Web site will not include information that can identify you. At most, the Web site will include a summary of the results. You can search this Web site at any time.
- If you would like to review the information for this study, or a summary of the results, ask the study team doctor for the ClinicalTrials.gov study registration number.
- During this study, you will not have access to certain medical information and test results collected for study purposes. If an emergency occurs while you are in the study, medical information needed for your treatment can be made available to your study physician and other physicians who treat you. When the study is completed, all the information in your medical record will be available to you.

2. Why is this research being done?

This research is being done to determine if giving insulin that is inhaled (intranasal insulin) is safe and tolerable for people with multiple sclerosis (MS). It is also being done to evaluate if intranasal insulin improves cognition in people with MS and to evaluate how it might be working.

Intranasal insulin (Novolin R®) has been approved by the Food and Drug Administration (FDA) for the treatment of diabetes. Intranasal insulin is not approved by the FDA to improve cognition in people with MS and its use in the study is considered investigational. The FDA is allowing for the intranasal insulin to be used in the study. The placebo contains inactive ingredients and is also approved for use.

People with MS who are aged 18 to 70 years and have some evidence of cognitive impairment may join.

How many people will be in this study?

105 people will be enrolled in the study.

3. What will happen if you join this study?

If you agree to be in this study, we will ask you to do the following things:

Study Summary

If you are able and choose to continue to take part in the study, then you will be randomly assigned (by chance, like drawing numbers from a hat) to receive one of three study products for 24 weeks:

- intranasal insulin 20 international units twice a day,
- intranasal insulin 10 international units twice a day, or
- intranasal placebo (an inactive material that does not contain any active study drug) twice a day.

You will then stop the study drug (intranasal insulin or placebo) and come back for follow-up visits for another 24 weeks.

About the Study Visits

You will be asked to come in to see the study team at the beginning of the study and at weeks 6, 12, 24, 36, and 48. For the first 15 participants, the first visit is expected to take about 4 hours. After enrollment of the first 15 participants, the visit is expected to take 2 ½ hours. The weeks 12, 24, and 48 visits are expected to be about 3 hours each. The remainder of the visits is expected to be about 1.5 hours each. You will be asked to not eat after midnight prior to the first visit but will be provided with breakfast after the blood draw.

Study Visits during the COVID-19 pandemic

During the periods of slowdown or shutdown, study visits at weeks 6, 36, and 48 will take place remotely. You will be asked to complete as many study procedures remotely as is possible (see asterisks below) for those visits. For the in-person study visits – baseline, week 12, and week 24, we have reduced

the in-person assessments to the greatest extent possible and have moved the rest to remote assessments. If the pandemic resolves, we will go back to an in-person study visit for week 48. If a stay-at-home order or severe outbreak recurs, we will also transition all possible study procedures for weeks 12 and 24 to remote assessments. During the COVID-19 pandemic, you must be willing to comply with state/local recommended social distancing and other suggested COVID-19 related safety measures.

About the Study Procedures

During the visits, you will have the following tests and procedures done as detailed below:

- **Teaching and first dose administration and observation of intranasal insulin:** At the baseline study visit, you will be taught how to prepare and administer the study products. You will receive four syringes filled with the study products – two labeled A and two labeled B. You or your caregiver will be instructed on how to fill the intranasal device cartridge using the syringes, mix the solutions and prep the device.

- ***Update medical record:** The study doctor or study coordinator will update your medical history and verify the medications you are taking and will ask you about any side effects.

- **Vital signs and examination:** Pending COVID-19, your vital signs will be taken at baseline, week 12 and week 24 study visits. A neurological examination will be conducted by the doctor at the first visit.

- ***Cognitive tests:** You will undergo a series of cognitive tests at all study visits except at weeks 6 and 36. Some or all of these will be done remotely at a given study visit.

- ***Questionnaires:** We will ask you to fill out questionnaires about how you are feeling at each study visit, as well as about your sleep at some of the visits.

- **Blood draw:** If COVID-19 restrictions allow in-person visits, you will be asked to give a blood sample at the baseline, week 12, and week 24 study visits. You will be asked to give up to 5 tablespoons of blood at each visit..

- **Pregnancy assessment/urine collection:** If you are a female and capable of having children, you will be asked to collect your own urine so a pregnancy test can be done at all in-person visits while taking the study medication. *During the COVID-19 pandemic, if assessments are remote, we will ask you to provide the date of your last menstrual period and information about use of contraception.

- **Dual-Energy X-ray Absorptiometry (DXA) scan:** A DXA is one type of x-ray often used to measure bone density. X-ray pictures of the body measure how much fat and muscle are present in your body. As you lie flat on a table, the machine takes pictures of different parts of the body. This test lasts about 15 minutes, and you will have this done at the baseline visit.

- ***Daily diary**: You will be required to keep a daily electronic diary. The purpose of the daily diary is to assess for side effects.

Request to collect and store biospecimens for future research

As part of this research study, we would like to ask you to let us store your biospecimens and health information for future research. This research could include other diseases and involve research tools such as gene sequencing or the creation of cell lines.

- Gene sequencing of your DNA provides researchers with the code to your genetic material.

- Cell lines are living tissue samples that can be grown in a laboratory. A cell line can provide an unlimited supply of cells in the future without requiring more samples from you. Each cell contains your complete DNA.

The study doctor can provide you with additional information if you have questions. Also, further information about our use of your biospecimens can be found in this consent document under the heading *What happens to Data and Biospecimens that are collected in the study?*.

Will you allow us to store the biospecimens we collect for this study for use in future research*?*

YES ☐ _____
Signature of Participant

NO ☐ _____
Signature of Participant

How long will you be in the study?
You will be in this study for 48 weeks.

4. What are the risks or discomforts of the study?

Intranasal insulin
Intranasal insulin has been shown to be safe and tolerable in other populations and patient groups, but it has never been studied in people with MS. The most common side effects related to irritation of the nasal passages. Giving insulin through the nose did not result in lower circulating glucose (sugar) levels in other studies, but the first 15 people in this study will be monitored for this potential risk by testing a fingerstick blood glucose level periodically for 90 minutes after the first dose of intranasal insulin.

Insulin, given by the more traditional subcutaneous (injected under the skin) route, has the following potential risks:

Hypoglycemia: Hypoglycemia means low blood sugar. Common symptoms of hypoglycemia include sweating, dizziness or lightheadedness, shakiness, hunger, a fast heartbeat, tingling of the hands, feet, lips or tongue, trouble concentrating, confusion, blurry vision, slurred speech, anxiety, irritability, or mood changes, or headache. Very low blood sugar can cause loss of consciousness (passing out), seizures, or temporary or permanent brain problems or death. You can treat mild low blood sugar (hypoglycemia) by drinking or eating something sugary right away (fruit juice, sugar candies, or glucose tablets). It is important to treat low blood sugar (hypoglycemia) right away because it could get worse and could lead to passing out (loss of consciousness), seizures and death.

Hypokalemia: Hypokalemia means low blood potassium. Hypokalemia can lead to breathing problems, low heartbeat, or death.

Allergic reaction: You could have an allergic reaction to insulin. Common symptoms of an allergic reaction include a rash all over the body, trouble breathing, a fast heartbeat, sweating, and feeling faint.

Weight gain or swelling of the arms and legs.

There is no known benefit of intranasal insulin, and thus there is no known risk of being in the placebo group. All patients who are already on a medication for MS will be allowed to continue that medication during the study.

Blood Draw
Taking blood may cause discomfort, bleeding or bruising where the needle enters the body. In rare cases, it may result in fainting. There is a small risk of infection.

Confidentiality
Despite the best efforts of the research team, there may still be a risk if information about you were to become known to people outside of this study.

Questionnaires
You may get tired or bored when we are asking you questions or you are completing questionnaires. You do not have to answer any question you do not want to answer.

DXA scan
DXA testing is painless and involves exposure to radiation. This research study includes exposure to radiation from x-rays or gamma rays. This radiation exposure is for research purposes only and is not part of your medical care. X-rays and gamma rays can damage cells, but at low doses, the body is usually able to repair these cells.

The radiation exposure that you will get in this research study is 0.001 rem (a rem is a unit of absorbed radiation). This is less than the 0.3 rem that the average person in the United States gets each year from natural sources like the sun, outer space, air, food, and soil. The risk from the radiation exposure in this research study is very small.

The radiation exposure described here is what you will get from this research study only. It does not include any exposure you may have received or will receive from other medical tests outside of this study that are a part of your medical care. Radiation risk builds up with each exposure. You should think about your own history of radiation exposure from tests (like x-rays or CT scans) in deciding about the radiation in this study. If you have questions about the total amount of radiation you will be receiving, you should ask your doctor.

5. Are there risks related to pregnancy?

The risks of intranasal insulin to pregnant women are unknown. If you are pregnant, planning to become pregnant, or are breastfeeding a child, you cannot participate in this study. Women who become pregnant during the study will stop the study. Radiation from a DXA scan may be harmful to an embryo or fetus.

All women capable of having children will be tested for pregnancy at each study visit (except for the last 2 study visits) by a urine test.

This research may hurt an embryo or fetus in ways we do not currently know.

6. Are there benefits to being in the study?

There may or may not be a direct benefit to you from being in this study. If you take part in this study, you may help others in the future.

7. What are your options if you do not want to be in the study?

You do not have to join this study. If you do not join, your care at Johns Hopkins will not be affected.

8. Will it cost you anything to be in this study?

You will receive a separate Insurance and Research Participant Financial Responsibility Information Sheet (Sheet).

This Sheet will give you the following information:

- The procedures, tests, drugs or devices that are part of this research and that will be paid for by the study (no cost to you).
- The procedures, tests, drugs or devices that will be billed to you and/or your health insurer. If you have health insurance, you will be responsible for any co-pays or deductibles not covered by your insurance.

9. Will you be paid if you join this study?

You will receive a parking coupon for all study visits.

You may be required to provide your social security number to be paid for taking part in this study. Federal tax law requires that you report your research payments when you file your taxes. If your total payments from Johns Hopkins exceed $600 per year, Johns Hopkins will report these payments to the Internal Revenue Service and you will receive a 1099-MISC form from us.

10. Can you leave the study early?

- You can agree to be in the study now and change your mind later.
- If you wish to stop, please tell us right away.
- Leaving this study early will not stop you from getting regular medical care.

If you leave the study early, Johns Hopkins may use or give out your health information that it has already collected if the information is needed for this study or any follow-up activities**.**

11. Why might we take you out of the study early?

You may be taken out of the study if:

- Staying in the study would be harmful.
- You fail to follow instructions.
- You become pregnant.
- The study is cancelled.
- There may be other reasons to take you out of the study that we do not know at this time.

If you are taken out of the study early, Johns Hopkins may use or give out your health information that it already has if the information is needed for this study or any follow-up activities**.**

12. How will your privacy be protected?

We have rules to protect information about you. Federal and state laws and the federal medical Privacy Rule also protect your privacy. By signing this form you provide your permission, called your "authorization," for the use and disclosure of information protected by the Privacy Rule.

The research team working on the study will collect information about you. This includes things learned from the procedures described in this consent form. They may also collect other information including your name, address, date of birth, and information from your medical records ([which may include information about HIV, drug, alcohol or STD treatment, genetic test results, or mental health treatment).

The research team will know your identity and that you are in the research study. Other people at Johns Hopkins, particularly your doctors, may also see or give out your information. We make this information available to your doctors for your safety.

People outside of Johns Hopkins may need to see or receive your information for this study. Examples include government agencies (such as the Food and Drug Administration), safety monitors, other sites in the study and companies that sponsor the study.

If you are in a cancer study that receives federal funding, the National Cancer Institute (NCI) now requires that we report identifiable information (such as, zip code) about your participation. You may contact the NCI if you have questions about how this information is used.

The Department of Defense (DoD) and the U.S. Army Medical Research and Materiel Command (USAMRMC) will have access to records for audit purposes.

We cannot do this study without your authorization to use and give out your information. You do not have to give us this authorization. If you do not, then you may not join this study.

We will use and disclose your information only as described in this form and in our Notice of Privacy Practices; however, people outside Johns Hopkins who receive your information may not be covered by this promise or by the federal Privacy Rule. We try to make sure that everyone who needs to see your information keeps it confidential – but we cannot guarantee that your information will not be re-disclosed.

The use and disclosure of your information has no time limit. You may revoke (cancel) your permission to use and disclose your information at any time by notifying the Principal Investigator of this study by phone or in writing. If you contact the Principal Investigator by phone, you must follow-up with a written request that includes the study number and your contact information. The Principal Investigator's name, address, phone and fax information are on page one of this consent form.

If you do cancel your authorization to use and disclose your information, your part in this study will end and no further information about you will be collected. Your revocation (cancellation) would not affect information already collected in the study, or information we disclosed before you wrote to the Principal Investigator to cancel your authorization.

13. Will the study require any of your other health care providers to share your health information with the researchers of this study?

As a part of this study, the researchers may ask to see your health care records from your other health care providers.

14. What treatment costs will be paid if you are injured in this study?

Johns Hopkins and the federal government do not have programs to pay you if you are hurt or have other bad results from being in the study. However, medical care at Johns Hopkins is open to you as it is to all sick or injured people.

The costs for any treatment or hospital care you receive as the result of a study-related injury that are not covered by a health insurer will be billed to you.

By signing this form you will not give up any rights you have to seek compensation for injury.

15. What other things should you know about this research study?

a. What is the Institutional Review Board (IRB) and how does it protect you?

The Johns Hopkins Medicine IRB is made up of:

- Doctors
- Nurses
- Ethicists
- Non-scientists
- and people from the local community.

The IRB reviews human research studies. It protects the rights and welfare of the people taking part in those studies. You may contact the IRB if you have questions about your rights as a participant or if you think you have not been treated fairly. The IRB office number is 410-955-3008. You may also call this number for other questions, concerns or complaints about the research.

When the Johns Hopkins School of Medicine Institutional Review Board (IRB) reviews a study at another site, that site (institution) is solely responsible for the safe conduct of the study and for following the protocol approved by the Johns Hopkins IRB.

b. What do you do if you have questions about the study?

Call the principal investigator, Dr. Mowry or Dr. Newsome at 410-614-1522. If you wish, you may contact the principal investigator by letter or by fax. The address and fax number are on page one of this consent form. If you cannot reach the principal investigator or wish to talk to someone else, call the IRB office at 410-955-3008.

c. What should you do if you are injured or ill as a result of being in this study?

If you think you are injured or ill because of this study, call Dr. Mowry or Dr. Newsome at 410-614-1522 during regular office hours.

If you have an urgent medical problem related to your taking part in this study, call Dr. Mowry or Dr. Newsome at 410-614-1522 during regular office hours and call the page operator at 410-955-4331 (http://www.hopkinsmedicine.org/uhs/after_hours.html) and ask to be connected to Dr. Mowry or Dr. Newsome after hours and on weekends.

d. What happens to Data and Biospecimens that are collected in the study?

Johns Hopkins and our research partners work to understand and cure diseases. The biospecimens and/or data you provide are important to this effort.

If you join this study, you should understand that you will not own your biospecimens or data, and should researchers use them to create a new product or idea, you will not benefit financially.

With appropriate protections for privacy, Johns Hopkins may share your biospecimens and information with our research sponsors and partners.

16. What does your signature on this consent form mean?

Your signature on this form means that: You understand the information given to you in this form; you accept the provisions in the form and you agree to join the study. You will not give up any legal rights by signing this consent form.

WE WILL GIVE YOU A COPY OF THIS SIGNED AND DATED CONSENT FORM

Signature of Participant	(Print Name)	Date/Time

Signature of Person Obtaining Consent	(Print Name)	Date/Time

I have received the separate Insurance and Research Participant Financial Responsibility Information Sheet.

Signature of Participant	(Print Name)	Date/Time

NOTE: A COPY OF THE SIGNED, DATED CONSENT FORM MUST BE KEPT BY THE PRINCIPAL INVESTIGATOR; A COPY MUST BE GIVEN TO THE PARTICIPANT; IF YOU ARE USING EPIC FOR THIS STUDY A COPY MUST BE FAXED TO 410-367-7382; IF YOU ARE NOT USING EPIC A COPY MUST BE PLACED IN THE PARTICIPANT'S MEDICAL RECORD (UNLESS NO MEDICAL RECORD EXISTS OR WILL BE CREATED).

ONLY CONSENT FORMS THAT INCLUDE THE JOHNS HOPKINS MEDICINE LOGO CAN BE USED TO OBTAIN THE CONSENT OF RESEARCH PARTICIPANTS.

DOCUMENTATION OF PHYSICIAN/MID-LEVEL PROVIDER CONSENT

My signature below indicates that I have discussed the risks, benefits, and alternatives, answered any questions, and believe the participant is able to make an informed choice to join the study.

Signature of Physician/Mid-Level Provider	(Print Name)	Date/Time

Signature of Participant	(Print Name)	Date/Time

NOTE: A COPY OF THE SIGNED, DATED CONSENT FORM MUST BE KEPT BY THE PRINCIPAL INVESTIGATOR; A COPY MUST BE GIVEN TO THE PARTICIPANT; IF YOU ARE USING EPIC FOR THIS STUDY A COPY MUST BE FAXED TO 410-367-7382; IF YOU ARE NOT USING EPIC A COPY MUST BE PLACED IN THE PARTICIPANT'S MEDICAL RECORD (UNLESS NO MEDICAL RECORD EXISTS OR WILL BE CREATED).

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