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

Patient I.D. Plate

RESEARCH PARTICIPANT INFORMED CONSENT AND PRIVACY AUTHORIZATION FORM

Protocol Title: **A randomized controlled trial of vitamin D supplementation in multiple sclerosis**

Application No.: **NA_00049137**

Sponsor: **National Multiple Sclerosis Society**

Principal Investigator: **Ellen M. Mowry, M.D., M.C.R.**
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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.

2. Why is this research being done?

This research is being done to study the effectiveness of vitamin D when given as an add-on to standard therapy with glatiramer acetate (Copaxone) to people with multiple sclerosis (MS).

The use of vitamin D in this research study is investigational. The word "investigational" means that vitamin D is not approved by the Food and Drug Administration (FDA) for the treatment of MS. The FDA is allowing the use of vitamin D in this study.

Glatiramer acetate is FDA approved for the treatment of MS.

Studies have suggested that people with MS who have lower vitamin D levels have more attacks of MS. In animals with an MS-like disease, giving vitamin D improves the disease. Some doctors of people with MS give them vitamin D already, although they don't know if it is helpful or not. It is not known if giving extra vitamin D to people with MS helps make the disease better or not. The Institute of Medicine recommends that every person take 600 international units (IU) of vitamin D3 each day. The study doctors want to know if giving a higher dose of vitamin D3, 5,000 IU each day, results in lower risk of MS attack or worsening.

Half of the people in this study will receive standard-dose vitamin D, and half will receive high-dose vitamin D. All participants in this study will receive called glatiramer acetate.

People aged 18 to 50, with certain types of MS who have had recent MS activity (as determined by the study doctors), may join.

People who have been exposed to certain MS medications or who have other contraindications will not be eligible.

How many people will be in this study?

One hundred seventy-two people will take part in the study at all sites. About 55 people will take part in this study at Johns Hopkins

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:

Before you begin the main part of the study…

You will need to have the following "screening" exams, tests or procedures to find out if you can be in the main part of the study:

• **Physical examination:** You will have a physical examination, similar to those done for regular medical care. A neurological examination will also be performed.

• **Medical chart review:** Your medical chart will be reviewed by the study doctors

• **Vitamin D assessment:** In order to be enrolled in this study, you must have had a Vitamin D level checked within the previous 30 days. If your level is below 15 ng/ml (Vitamin D deficient), you will not be able to enroll in the study. If you wish to take Vitamin D supplementation and be retested and rescreened for enrollment, please discuss with your neurologist.

• **Blood draw:** You will be asked to give a blood sample for laboratory tests. Less than 1 tablespoon of blood will be drawn by inserting a needle into a vein in your arm for these tests.

• **Genetic study:** You will be asked to read a consent form for an additional genetic study. This study will be done to help doctors understand how vitamin D influences the immune system in MS. You are not required to participate in the genetic study.

• **Pregnancy testing:** Because it is unknown if the drugs in the study can affect a fetus, pregnant women cannot participate in the study. A urine test will therefore be done, if you are a woman, to make sure you are not pregnant.

• **Starting glatiramer acetate:** If the screening exams, tests or procedures show that you can be in the study, you will come in for an additional visit and start glatiramer acetate (Copaxone) injections for MS. This is a standard treatment for MS, and you will continue it during the study. If you take the glatiramer acetate for a month without difficulties, you will be eligible to continue for the main part of the study.

During the main part of the study…

If you are able and choose to continue to take part in the study, then you will be randomly assigned (by chance, like the flip of a coin) to receive either 5,000 IU daily (high dose) or 600 IU daily (standard dose) of oral vitamin D_3.

You will be asked to come every three months for a study visit. Some visits will be short (months 3, 6, 9, 15, 21), lasting about 30 minutes. The baseline, year 1, and year 2 visits will be longest, lasting about 2 ½ to 3 hours. The remainder of the visits will take about 1 to 1 ½ hours.

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

• **Start taking vitamin D supplements:** You will be given a sufficient supply of vitamin D_3 capsules at each visit to last until the next visit. You will take one capsule each day. You will need to bring the pill bottle with you to each study visit.

While in this study, you may not take any additional vitamin D supplements, nor may you take cod liver oil.

• **Update medical record:** The study doctor or study coordinator will update your medical history and verify the medications you are taking. They will also check to see whether you have been able to take the medications associated with the study.

• **Physical examination:** A physical examination will be conducted at the baseline visit and once a year

• **Neurological examination:** A neurological examination will be conducted by the doctor at the baseline visit and once a year after that. Additional neurological and vision testing will be conducted by the study coordinator every six months.

• **Questionnaire:** We will ask you to fill out questionnaires determining your sun exposure habits have been and about how you are feeling periodically.

• **Blood draw:** You will be asked to give a blood sample every three months during the study. Up to 2 tablespoons of blood will be drawn by inserting a needle into a vein in your arm for these tests. If you participate in the genetics study, approximately 3 tablespoons of blood will be taken at the baseline visit and 2 tablespoons of blood will be taken at the year 1 and year 2 visits.

• **MRI:** At the baseline study visit and at the year 1 and year 2 study visits, you will have an MRI scan of the brain. In order to ensure the MRI scan quality is sufficient, we will do a dry-run MRI scan on one individual. You may be asked to allow for your baseline scan to be used as the dry-run for quality purposes. This will not result in having an additional MRI. The MRI exam will take approximately 1 ½ hours. Prior to your exam, you will be asked to complete a standard questionnaire. The purpose of this questionnaire is to ensure that you are able to safely enter the MRI area. If you have a history of metal in your head or eyes, you cannot take part in this study.

To start your MRI test, you will lie on a padded table. The table on which you are lying will be moved to the center of an MRI magnet, which looks like a long narrow tube. Even though the tube is open, some people feel confined in small places. If this bothers you, please notify the MRI staff. You may end your participation in this study at any time by telling the MRI staff. When MRI pictures are taken, radio-signals and magnetic fields are used. When this happens, it is normal for the MRI machine to make loud, banging, and clicking noises. You will be asked to wear earplugs or headphones for your comfort during the exam.

During the exam, the MRI staff is able to see and hear you. You will be able to hear the MRI staff. The MRI staff will be talking to you throughout your MRI exam and may issue simple instructions regarding holding your breath, maintaining position, etc. You will generally be requested to lie perfectly still throughout the exam.

At some point during your MRI exam the MRI staff will interrupt the scanning procedure in order to give a contrast agent. The agent is given through a needle placed (an IV) in your arm. The IV will be placed using standard hospital techniques.

Incidental Findings

The MRI you are having as part of this research study will be reviewed by a qualified person just as it would be if you were having the MRI as part of your routine medical care.

There is a possibility that while reviewing MRI we may see an abnormality that we did not expect to see in this study. This is what is called an "incidental finding."

We will let you know if we see such an incidental finding. Depending on the type of incidental finding, we may contact you by mail or by phone. In the case of a potential serious emergency, someone may go to your home.

A qualified person (usually a member of the research team) will talk to you if there is an incidental finding. You do not have an option to decline information about an incidental finding.

If you want, we will give information about this incidental finding to your primary doctor or we will refer you to an appropriate doctor for further evaluation.
- An incidental finding may cause you to feel anxious.
- Since an incidental finding will be part of your medical record, you could face greater difficulty in getting health or life insurance.
- The costs for any care that will be needed to diagnose or treat an incidental finding would not be paid for by this research study. These costs would be your responsibility.

• **Communication with study coordinator:** A study coordinator will call or e-mail you periodically to determine how you are doing with the study medicines, whether you are having new symptoms, and to remind you about appointments.

• **Additional visits:** If you are having neurological symptoms that are concerning for an MS relapse or if you are having any symptoms concerning for side effects, you should report them to the study doctor within 48 hours. You may be asked to come within the next three days for an examination. If so, you will be examined by the study doctors. If they think it is necessary, you may be given treatment to help with the relapse symptoms. The treatment would not be paid for by the study.

• **Communication with your doctors:** We will inform your primary care doctor and your neurologist at the beginning of the study that you have enrolled in the study so that they know you are taking vitamin D and glatiramer acetate.

During the COVID-19 pandemic, we may conduct some of the study assessments on an altered schedule or provide some of the assessments remotely, in accordance with institutional guidelines and the principal investigator's goal to minimize risk.

Storage and Use of Samples
The study will involve storage of blood samples for future research at the baseline visit and at months 3, 6, 12, 18, and 24. These samples will be used to test vitamin D levels at the end of the study and to see what effects vitamin D has on the immune system.

How long will you be in the study?
You will be in this study for two years.

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

Vitamin D (cholecalciferol)
Vitamin D toxicity can result from excess intake of this vitamin, and may lead to high calcium levels (hypercalcemia). Individuals at particular risk include those with hyperparathyroidism, kidney disease, sarcoidosis, or tuberculosis. Chronic hypercalcemia may lead to serious or even life-threatening complications, and should be managed by a physician. Early symptoms of hypercalcemia may include nausea, vomiting, and appetite/weight loss, followed by excess urination, excess thirst, weakness, fatigue, somnolence, headache, dry mouth, metallic taste, vertigo, ear ringing, and unsteadiness on your feet. Kidney function may become impaired, and kidney stones can occur. Treatment involves stopping the intake of vitamin D or calcium, and lowering the calcium levels under strict medical supervision, with frequent monitoring of calcium levels.

Glatiramer acetate (Copaxone)
The most common side effects are irritation, redness, itchiness, pain, or swelling at the injection sites. Bruising may occur with injections. There is a small risk of infection associated with the injections Some people rarely report a sensation of anxiety, agitation, flushing, rapid heartbeat, or chest pain upon injecting the medication. These symptoms should go away within minutes. A rare but serious risk is that of an allergic reaction, in which rash and trouble breathing can occur. Over the long term, changes in the skin can occur that make it look lumpy.

Magnetic Resonance Imaging (MRI) Examination
The effects of magnetic fields in an MRI scanner have been extensively studied, and there are no known significant risks with an MRI exam. You may, however, be bothered by feelings of confinement (claustrophobia), and by the noise made by the magnet during the procedure. You will be asked to wear

earplugs or earphones while in the magnet. You may not participate in this study if you have a pacemaker, an implanted defibrillator or certain other implanted electronic or metallic devices. It is important for you to advise the MRI staff if you have had brain surgery for a cerebral aneurysm, or if you have implanted medical or metallic devices, shrapnel, or other metal, such as metal in your eye.

MRI Contrast Agent

The contrast agent you will receive is FDA-approved and used routinely for MRI exams. It contains a material called gadolinium. The injection of contrast may cause discomfort, tingling or warmth in the lips, metallic taste in the mouth, tingling in the arm, nausea, or headache. These symptoms occur in less than 1% (less than 1 in 100) of people and go away quickly.

There is a small risk of an allergic reaction to gadolinium; however, a severe allergic reaction occurs in less than one in 300,000 people.

Insertion of the needle (small plastic tube) to give you gadolinium may cause minor pain, bruising and/or infection at the injection site.

People with severe kidney failure who receive gadolinium are at risk of developing Nephrogenic Systemic Fibrosis/Nephrogenic Fibrosing Dermopathy (NSF/NFD). This disease causes fibrosis, which is the formation of too much connective tissue in the skin and internal organs throughout the body. People develop skin thickening that may prevent bending and extending joints, resulting in decreased movement of the joints. The skin changes can cause feelings of burning, itching and pain that can be severe. In addition, people may experience fibrosis that spreads to other parts of the body such as the diaphragm, muscles in the thigh and lower abdomen, and the lining of blood vessels in the lung. NSF/NFD is a serious progressive disease and can result in death.

If you have severe kidney failure and receive gadolinium, the risk of developing NSF/NFD is 1-5 % (up to 1 to 5 per 100 people). We may require a blood sample (about 1 tablespoon) to check your kidney function before you receive gadolinium contrast for your MRI.

Please notify a doctor, nurse or technologist if you are allergic to gadolinium, if you have any kidney problems, or if you experience any of these or other side effects. If you do not know if you have kidney problems or if you do not know if your kidney problems fall in the severe category, you can ask the principal investigator of your study to give you this information.

A doctor will be available during the procedure to administer any necessary care if side effects do occur, and to determine when or if the injection of the gadolinium should be stopped.

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 protections and 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.

There may be side effects and discomforts that are not yet known.

5. Are there risks related to pregnancy?

There are no known risks of vitamin D or glatiramer acetate in pregnancy. Glatiramer acetate is used by some doctors during pregnancy, and vitamin D has been shown to be safe for pregnant women. Nonetheless, these medications will be stopped for anyone who becomes pregnant in the research study as a safety precaution.

All women of childbearing potential will be tested for pregnancy at each study visit by a urine test.

All women in the research study will be asked to use one or more forms of birth control if of childbearing potential.

MRI imaging is not known to cause risk to the developing fetus though there may be risks that are not known at this time. MRI contrast is known to cross the placenta and subsequent risks to the developing fetus are not known.

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. However, you may help future people with MS know if vitamin D makes the disease better

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

You do not have to participate in the study. If you decide not to join this study, other options are available. You do not have to join this study to get treatment. Other treatments include being prescribed a treatment through your regular neurologist or joining another research study, if you qualify. You could also take vitamin D without joining 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?

No.

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 already has 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 need treatment not allowed in the study.
- 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. This could include information about HIV, drug, alcohol or STD treatment and 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.

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.

- You will be asked to give us a list of other health care *providers*, particularly the neurologist that you use.

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

Johns Hopkins does not have a program 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.

If you are a participant at Anne Arundel Medical Center, you may contact the AAMC IRB office at 443-481-1320.

b. What do you do if you have questions about the study?
Call the principal investigator, Dr. Ellen Mowry at 410-502-0675. If you wish, you may contact the principal investigator by letter at 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.

If you are taking part at Anne Arundel Medical Center, call Dr. Arash Farhadi at 301-922-6683.

c. What should you do if you are injured or ill as a result of being in this study?
Call the study doctor, Dr. Ellen Mowry at 410-502-0675 if you have an urgent medical problem related to your taking part in this study. If you cannot reach the study doctor or wish to talk to someone else, call the IRB office at 410-955-3008.

For 24 hour assistance please contact the Johns Hopkins Hospital Page Operator which at (410) 955-4331 (http://www.hopkinsmedicine.org/uhs/after_hours.html) and ask to be connected to Dr. Mowry.

If you are taking part at Anne Arundel Medical Center and you have a medical problem related to your taking part in this study, call Dr. Arash Farhadi at 301-922-6683. If this doctor is not available, the operator will page the "on call physician."

d. What happens to Data and Biospecimens 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
- 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, LAR or Parent/Guardian	(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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