THE UNIVERSITY OF NEW MEXICO HEALTH SCIENCES CENTER
CONSENT TO PARTICIPATE IN RESEARCH

Study Title	**Double-blind, placebo-controlled, randomized study of the safety and tolerability of isoxsuprine HCL combined with high dose steroid treatment of multiple sclerosis (MS) relapse**
Protocol Number	D3RN Clinical Study Proposal
Principal Investigator (PI)	Clotilde Hainline, MD
Name of Research Center	University of New Mexico
PI Phone Number	505-272-8905
PI Address	1101 Yale Blvd NE; Albuquerque, NM 87131

Introduction

You are being asked to participate in a research study being done by Clotilde Hainline MD, who is the Principal Investigator and associates, from the Department of Neurology.

This consent form describes the research study to help you decide if you want to participate. Before agreeing to be in this study, it is important that you read this form, and the HIPAA Authorization.

If you sign this form, it means that you agree to take part in this study. This form describes the study and what will happen if you are in the study. It also tells you about the risks and benefits of the study.

Please read this form carefully. You will be given ample time to read and review this form. You may discuss this study with family and friends. You will have an opportunity to ask the study staff about any of your questions or concerns regarding the research study.

If you have a personal or primary care doctor, we suggest that you inform their office of your participation in this research study.

This consent form may contain words that you do not know. Please ask the study doctor, or the study staff to explain any words, or information that you do not clearly understand.

CTSC (Clinical & Translational Science Center) at UNM is funding this pilot study.

When deciding to take part in a research study you should know:

- The main goal of medical care is to help you.
- The main goal of a research study is to gain information to help patients in the future.
- Parts of this study may involve medical care that is routine for you. This routine care, known as standard care, is the treatment normally given for a certain condition or illness.
- Being in this study does not replace your regular medical care.

This study was approved by The University of New Mexico Human Research Review Committee.

You will be asked to sign and date this form, if you decide to be in this study; you will also get a copy of the form to keep, after you have signed. The signed and dated original will be given to the Investigator and will remain at the site with your file.

Purpose

The purpose of this study is to examine the safety and tolerability of Isoxsuprine (ISX) in combination with high dose oral prednisone in subjects experiencing acute relapses due to multiple sclerosis. Studies of isoxsuprine done at this university in animals show that the drug can reduce damage to the brain caused by a stroke. This effect is referred to as neuroprotection (protecting the nervous system from injury). Since ISX is a safe, approved medication used in people for other reasons, we want to know if it might help people with MS who are having a relapse. Before we test the drug for any neuroprotective benefits, we need to show that it is tolerable and safe to take during an MS relapse that is also being treated with steroids.

Isoxsuprine hydrochloride (ISX), study medication, or study drug in this document is a compounded capsule with identical placebo, 10 mg by mouth 3 times per day for 5 days.

This research study will use ISX and placebo. A placebo is an inactive treatment that looks the same as ISX, and is given the same way as ISX. The placebo has no active ingredients. In this Informed Consent Form, the term “study drug” refers to either ISX or placebo.

You are being asked to be in this study because you are 18 years old or older; have a relapsing form of multiple sclerosis, and are currently having a relapse and willing to

take high dose oral prednisone (a corticosteroid). About twenty people will be invited to take part in this study at the University of New Mexico.

Study Requirements

The study doctor or study staff will review your current list of medications, supplements, and your medical history, to decide if there is anything that may prevent you from being in this study.

The study doctor, and staff will ensure for instance, that:

- You are 18 years old or older
- Your blood pressure is stable

You are expected to follow the directions of the study doctor, and the study staff as closely as you can. Some of these directions are:

- Complete all required visits to the research center
- Take the study drug as instructed by the study doctor
- Give urine samples if you are a female of child bearing potential
- Tell the study staff about all of the medicines you take during the study
- Report all side effects and medical problems to the study doctor or the study staff
- Not allow anyone else to use your study drugs
- Inform the study doctor, or staff if you decide, you no longer wish to participate in the study.

Study Restrictions

You should not participate in this study if you:

- Have a history of hypersensitivity or allergic reaction to any of the study drugs, prednisone or isoxsuprine.
- Poorly controlled type 1 or type 2 diabetes mellitus
- Have any known contraindication(s) to taking isoxsuprine hydrochloride (ISX), including, but not limited to:
    - any current uncontrolled hypertension, primary adrenal gland insufficiency
    - Any current psychoses, infectious disease, or Cushing's syndrome. (Cushing's syndrome is a diagnosis caused by overproduction of corticosteroid hormones by your adrenal gland. If you have this condition you will not be able to participate in this study.)
    - Any current congestive heart failure (defined as New York Heart Association (Functional Class III to IV).

    - Peptic ulcer (within 24 weeks prior to the Screening Visit).
    - Recent major surgery
- History of myocardial infarction (heart attack)
- If female, is pregnant or breast feeding;
- Chronic use of corticosteroids except low dose for asthma or related illnesses

Study Termination

Your participation in this study can be stopped by the study doctor or the Human Research Review Committee (HRRC), without your permission for any of the following reasons at any time:

- If the study drug or procedures seem harmful to you;
- If you do not follow directions for being in the study;
- If it is discovered that you do not meet the study requirements;
- If the study is canceled;
- If you need treatment that is not allowed in the study;
- If you become pregnant;
- For other reasons that are unknown at this time.

If the study doctor stops you or you decide not to continue being in the study, all study data to that point will be reviewed.

What will happen if I decide to participate?

You must sign and date this Informed Consent Form before any tests and exams can be performed.

You will first complete a 'Screening' evaluation so that your doctor can check that you are suitable for the study. After being selected for the study, you will be randomly assigned (like flipping a coin) to receive high dose oral prednisone to treat your MS relapse plus one of the two following treatments:

- Treatment A: Isoxsuprine HCL (ISX)1 Capsule 3 times per day for 5 consecutive days, Or
- Treatment B: Placebo 1 Capsule 3 times per day for 5 consecutive days.

You and your doctor will not know which treatment group you are in. You, or study staff will administer the first dose of study drug in the clinic under the supervision of study staff. You will remain in the clinic for at least 1 hour after taking the study drug so the study staff can monitor you for any allergic or anaphylactic reactions; afterwards, you or your caregiver will administer all doses at home.

The study drug is supplied as a 10 mg capsule, to be taken three times daily for five days in addition to high dose corticosteroid 600mg twice a day (oral prednisone). The study drug will be supplied to you by the study doctor.

This research study involves a Screening and Randomization visit; Weeks 1, 4, and 12 (4 visits total).

Screening Visit (Visit 1)

After signing the Informed Consent Form, you will have tests and procedures done, to determine if you are able to continue to take part in this research study.

At the first visit, screening tests and procedures will be done. The study doctor will ask some questions about you, your general health, and your medical history. These tests do not guarantee that you will be able to take part in this research study; your participation in this study will depend on study guidelines.

The following procedures will be performed at your screening visit:

- Review Eligibility Criteria; you must meet all eligibility criteria;
- Vital signs (blood pressure taken 3 times, breathing rate, heart rate, and temperature), including height and weight;
- Physical examination, which includes evaluation of your lungs, heart, abdomen, and extremities;
- Complete Memory and Physical Function Tests, and whether or not you are having any problems;
- Perform 12 Lead Electrocardiogram (ECG)
  An ECG is a measurement of the electrical activity of your heart.
- Neurological Exam
- Review medications you are currently taking (concomitant medications).

Randomize (Visit 1)

Once screening procedures are completed, and you are found to be eligible to enter the study, you will be randomized to either group A or group B and the study doctor will ask you to either take oral prednisone (1,200 mg each day), for 3 to 5 days or to continue taking the prednisone already prescribed to you by your Neurologist.
The following procedures will be performed:

- 12-lead electrocardiogram (ECG) post dose;
- Urine pregnancy test (if you are a woman who can become pregnant);
- Study drug will be given, under the supervision of study staff, and you will be asked to remain in the clinic for observation for at least 1-hour thereafter;
- Review adverse events (AEs), and concomitant medications.

You must stay under supervision of the study staff for at least 1-hour after the first dose of study drug; you will be given study drug to take home afterwards to be taken three times daily for five days.

1 Week Post Treatment Safety Follow-Up Visit (Visit 2) Procedures/Assessments

The following procedures will be performed at this visit:

- Physical examination;
- Neurological exam;
- Physical Function Tests;
- Vital signs;
- Adverse events and concomitant medications;

4 Week Post Treatment Safety Follow-Up Visit (Visit 3) Procedures/Assessments

The following procedures will be performed at this visit:

- Physical examination;
- Neurological exam;
- Complete Memory and Physical Function Tests;
- Vital signs;
- Adverse events and concomitant medications;

12 Week Post Treatment Safety Follow-Up Visit (Visit 4) Procedures/Assessments

The following procedures will be performed at this visit:

- Physical examination;
- Neurological exam;
- Complete Memory and Physical Function Tests;
- Vital signs;
- Adverse events and concomitant medications Adverse events and concomitant

Study Drug Handling

You are only allowed to use ISX which should be kept at room temperature.

It is your responsibility to:

- Keep the study drug in a safe place;
- Tell the study doctor, or study coordinator if any study drug is stolen, or lost;
- Take study drug only as directed by the study doctor;
- Stop anyone else from using the study drug meant for you.

How long will I be in this study?

Subjects will participate in the study for a total of up to 12 weeks. Study visits include a screening/randomization visit with drug administered and safety and efficacy assessment visits at week 1 (7 days after completion of ISX dosing), week 4 and week 12.

What are the risks or side effects of being in this study?

Risks are possible including side effects of study treatment and from tests done during the study. All medications can have side effects (adverse events) and there are always potential risks, discomfort and inconvenience associated with participation in a research study. This is why the physical examinations and other tests that you will undergo during this study are important. If there are unwanted effects related to the study medication, they will be detected as early as possible and your Study Doctor can take steps to prevent you from harm.

You must tell the study doctor, or study staff about any side-effects you experience. If you do not tell the study doctor and study staff about the side effects, you may harm yourself by being in this study. Do not stop taking the study medication without first talking to your study doctor, even if you are experiencing side effects.

Taking a placebo may be similar to not taking any medication. Whether you are taking a placebo or taking ISX, your symptoms may stay the same or get worse. You will be allowed to continue taking your current treatment while you are participating in this study. The Prednisone tablets you will take are a standard high steroid dose commonly given to help speed recovery of your MS relapse symptoms as standard of care.

Other possible side effects

Along with its needed effects, isoxsuprine may cause some unwanted effects. Although not all of these side effects may occur, if they do occur they may need medical attention.
Check with your doctor as soon as possible if any of the following side effects occur while taking isoxsuprine:

Rare

- Chest pain
- dizziness or faintness (more common for injection)
- fast heartbeat (more common for injection)
- shortness of breath
- skin rash

Some side effects of isoxsuprine may occur that usually do not need medical attention. These side effects may go away during treatment as your body adjusts to the medicine. Also, your health care professional may be able to tell you about ways to prevent or reduce some of these side effects. Check with your health care professional if any of the following side effects continue or are bothersome or if you have any questions about them:

Less Common

- Nausea or vomiting (more common for injection)

Treatment with study drug should be discontinued if any of the following occur:

- Development of accelerated hypertension (defined as systolic blood pressure ≥ 180 and diastolic blood pressure ≥ 100 mm Hg) that cannot be managed by the adjustment of concomitant medications such as antihypertensive medications.
- Development of symptomatic hypotension (defined as syncope or orthostatic lightheadedness) or systolic blood pressure ≤ 100 and diastolic blood pressure ≤ 50 mm Hg).
- Development of congestive heart failure that cannot be managed by the adjustment of concomitant medications such as diuretics and antihypertensive medications.
- Development of diabetic signs/symptoms or classic symptoms of hyperglycemia with random plasma glucose> 200 mg/dL).
- Development of any other AE of at least moderate intensity and possibly, probably or definitely related to study drug that cannot be managed by the adjustment of concomitant medications.

You should call the numbers provided or get medical help, if you have any of these or any other side effects during the study.

Reproductive Risks

Females

Study drug taken during pregnancy may cause you to lose your unborn baby. Additionally, it is not known if the study drug can be in the mother's breast milk. Therefore, you cannot be in this research study if:

- You are pregnant ;
- You are planning to become pregnant during the next couple of months;
- You are breastfeeding.

If you agree to be in this research study, and are able to get pregnant, you must take some steps to keep yourself from getting pregnant during the entire study.

You should use at least one method of birth control like the examples below:

- Hormonal measures (birth control pills, contraceptive patch, contraceptive ring, injections);
- Intrauterine device (IUD);
- Double barrier method (condom plus diaphragm, condom or diaphragm plus spermicidal gel or foam);
- Abstinence.

If you have any questions about birth control, please ask the study doctor or study staff.

If you suffer any of these side effects (or any others not listed) or you think you are experiencing a side effect, during this study, please tell your study doctor immediately.

For your own safety, you must tell the study doctor the truth about your past and present health. You should also tell the study doctor about:

- Disease and medical conditions;
- Mental health conditions;
- Allergies;
- Medicines used during the study, including medicines you use that do not require a prescription (examples: Vitamins, aspirins, and herbal medicines).

If you are not truthful about your past or current health, you may be harmed by being in this study.

Unknown Risks

In addition to the risks of the study that are listed above, there may be other risks that are unknown and can't be predicted. These risks may include allergic reactions or other side effects caused by mixing the study medication with other medicines or supplements you may be taking.

If you have any concerns, you should tell the study doctor or study staff right away.

Your safety will be closely monitored throughout the study.

What are the benefits to being in this study?

You may or may not benefit from participating in this study. ISX will not cure your multiple sclerosis but if you receive it in this study, it may lessen your MS symptoms and help you recover sooner or more completely from the relapse. However, taking part in this clinical study might not benefit you in any way and the study drug may not help you. Your taking part may give more scientific information about ISX and its possible role in relapsing forms of multiple sclerosis. This information may help others in the future. You will have a 50:50 chance (like the flip of a coin) of receiving isoxsuprine or placebo. A computer will randomly assign you to receive either ISX or placebo and neither you nor the study staff or investigator will know what you have been given until the study is over.

What other choices do I have if I do not want to be in this study?

Corticosteroids like Prednisone are not considered effective long term treatments for MS but other treatments for MS are available. You may be on one of these now or might decide to start one after you complete this study. These treatments have been shown to be effective in reducing the number of relapses suffered by patients, in some cases

prolonging the time before a worsening in disability occurs. Relapses of MS do not have to be treated with Corticosteroids like Prednisone and recovery can occur naturally. However, it has been shown that the use of Corticosteroids can shorten the time to recovery or improvement. You may choose to receive the standard Prednisone dose alone without enrolling in the study. In this case the study doctor will write a prescription for you to take to your pharmacy.

The study doctor will be happy to discuss MS treatment options with you to help you determine if they are appropriate. At the end of the study, you and your study doctor will discuss your future care options including any additional care you may need that is beyond what you would normally receive for your MS.

Being in this study is voluntary. This means you can decide if you do or do not want to be in the study. There will not be any penalty or loss of benefits or standard of care treatment to you if you decide not to take part or if you leave the study early. If you decide to be in this research study, you can stop participation at any time, as there is no penalty or loss of benefits for doing so. If you want to withdraw from this study, please inform the study doctor. If you decide to leave the study early, there may be risks with this decision. You should discuss these risks with your study doctor. You may be asked to return to the clinic for tests.

How will my information be kept confidential?

We will take measures to protect your privacy and the security of all your personal information, but we cannot guarantee confidentiality of all study data.

Your records will be identified by the study subject number (according to local law). Your name will not be used in any study reports, and these reports will be used for research purposes only. UNM and its designee(s), the Human Research Review Committee (HRRC)and various government health agencies (such as the FDA) may inspect and/or copy your records of this study Information about your disease status and may be requested and reviewed on a regular basis after you have completed all visits in this study. A copy of this consent form will be kept in your medical record.

Every effort will be made to keep your personal medical information confidential. We cannot guarantee absolute confidentiality. Your personal information may be disclosed, if required by law. In addition, results from this study may be published. In such a case, your identity will still be confidential, but the results of the study will be more widely distributed**.**

By signing this consent form, you are giving permission for this, as well as for processing and transferring your coded personal information relevant to this trial. You are also giving permission for processing of your coded personal information in a database.

You may use your rights under the local data protection law to access and correct your personal information or ask for it to be deleted. You can object to any further processing of your information by applying to the study doctor.

The study doctor may tell your family doctor about your taking part in the study and ask them for medical information about you

There is a risk of loss of confidentiality in research studies. Every effort will be made to protect you and your health information to the extent possible.

A description of this study 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 results. You can search this website at any time.

What are the costs of taking part in this study?

This study will supply the study drug needed for treating your relapse while you participate, at no cost to you. Many of the study tests (urine tests and ECG) and the steroid treatments are part of the standard evaluation and care for the treatment of your disease. UNM CTSC will pay for all study-required procedures that are above and beyond standard of care. This includes the costs of study related tests that are not covered by your health insurance company. Your health insurance company will be billed for the costs of these tests that are not covered by the study. The costs of those tests will be paid in the same way as if you were not part of this study.

Will I be paid for taking part in this study?

You will not be compensated for your participation this study.

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

It is important that you follow carefully all the instructions given by the Study Doctor and his/her staff regarding this study.

If you become ill or are physically injured as a result of participation in this study, please contact the Study Doctor right away: Clotilde Hainline MD, at (505) 272-3160, (505) 272-0356 or (505) 272-2111; she will treat you or refer you for treatment.

If you are injured or become sick as a result of this study, the UNM HSC will provide you with emergency treatment.

If the study was done correctly and you were hurt by the study drug, UNMHSC will pay for all reasonable medical bills that your insurance company does not pay. UNMHSC

will only pay these bills if you received reasonable medical care. These are the only bills that UNMHSC will voluntarily pay.

UNMHSC will not pay your medical bills if:

- you did not follow instructions,
- your disease or the standard treatment of your disease caused your harm.

Contact the study staff if you think that being a subject in this study has caused you to be harmed. The study staff will tell you how you can get medical care for your problem.

You or your insurance company will be charged for continuing medical care and/or hospitalization required for any such injury or illness not related to the research study.

By signing this consent form, you will not give up any legal rights.

Study Contacts

You can call Dr. Clotilde Hainline at (505) 272-3160 or the research coordinator at (505) 272-8905 from 8:00 AM to 4:30 PM Monday through Friday, if you feel that you are developing any undesirable or unwanted effect (adverse event), if you believe you have been injured as a result of receiving study drug, or if you have any questions about this study. We will give you a card to carry with contact information and numbers in case of an emergency.

If you need to contact someone after business hours or on weekends, please call (505) 272-2111 and ask for Dr. Clotilde Hainline or the faculty Neurologist on call.

If you have any questions about your rights as a research subject, questions about participation in the study, or complaints about the study, you may contact someone independent from the study at UNMHSC HRRC at (505) 272-1129.

Whom can I call with questions or complaints about this study?

If you have any questions, concerns or complaints at any time about the research study, Clotilde Hainline MD, or her associates will be glad to answer them at (505) 272-3160

If you need to contact someone after business hours or on weekends, please call (505) 272-2111 and ask for Dr. Hainline or the faculty Neurologist on call.

If you would like to speak with someone other than the research team, you may call the UNMHSC HRRC at (505) 272-1129.

Whom can I call with questions about my rights as a research subject?

If you have questions regarding your rights as a research subject, you may call the UNMHSC HRRC at (505) 272-1129. The HRRC is a group of people from UNM and the community who provide independent oversight of safety and ethical issues related to research involving human subjects. For more information, you may also access the HRRC website at http://hsc.unm.edu/som/research/hrrc/.

Statement of Consent

I have read the information in this consent form. I have had a chance to ask questions and my questions have been answered to my satisfaction. I voluntarily agree to be in this study until I decide otherwise. I do not give up any of my legal rights by signing this consent form. I will receive a copy of this signed document.

Printed Name of Subject

Signature of Subject | Date

By signing below, I also authorize Dr. Clotilde Hainline or designee to contact me after the study ends to request additional information or to participate in additional studies that might be developed from the results of this study.

Printed Name of Subject

Signature of Subject | Date

Investigator/Designee:

- ✓ I have fully and carefully explained the study to the person named above in language he/she understands and confirm that, to the best of my knowledge, they clearly understand the nature, risks and benefits of taking part in this study.
- ✓ I confirm that I gave them a chance to ask questions about the study and that I answered all the questions they asked correctly and to the best of my ability.
- ✓ I confirm that they have not been forced into giving consent and that they have given their consent freely and voluntarily.
- ✓ I confirm they have been given a copy of this information sheet and consent form.

Printed Name of Person Obtaining Consent:

Signature of Person Obtaining Consent: Date