Consent Form

Study Title: Treatment of progressive forms of Multiple Sclerosis with pulsed ACTH (Acthar gel)

Principal Investigator: Adam Carpenter, MD
University of Minnesota, Department of Neurology
717 Delaware Street SE, Suite 246
Minneapolis, MN 55414

Introduction
You are invited to participate in a research study to examine how safe and effective ACTH (adrenocorticotropic hormone, Acthar gel) is in patients with progressive forms of Multiple Sclerosis (MS). You were chosen as a possible participant because you have been diagnosed with Primary Progressive MS (PPMS), Secondary Progressive MS (SPMS), or Progressive Relapsing MS (PRMS). This consent form describes the research study and what you may expect if you decide to participate. Please read this consent form carefully and ask any questions you may have before you decide if you want to participate.

This study is being conducted by Dr. Adam Carpenter at the University of Minnesota. It is funded by Mallinckrodt Pharmaceuticals, the manufacturer of ACTH. Approximately 100 people will participate in this study.

Study Purpose
The purpose of this study is to investigate the safety and effectiveness of ACTH in progressive MS patients when it is administered on a pulsed schedule of injections on three consecutive days per month. ACTH is approved by the US Food and Drug Administration (FDA) for the treatment of MS relapses. In this study, we are looking at whether pulsed ACTH is safe and well-tolerated in progressive forms of MS, as well as whether or not it can slow the progression of MS. ACTH is considered an "investigational drug" in this study, because it has not been approved specifically for this use by the FDA.

Study Procedures
Approximately 100 patients with PPMS, SPMS or RPMS will participate in this study at research sites in Minnesota and the Midwest. If you choose to participate, you will be in the study for 3 years, and you will come to the Clinical Neuroscience Research Unit (CNRU) for up to 9 study visits. You will be assigned by chance (like flipping a coin) to inject either 80 units of ACTH or placebo (an injection that contains no medicine). You or a caregiver will administer the injection subcutaneously (under the skin) on 3 consecutive days per month. Neither you nor the study team will know which treatment group you are in, although in an emergency the exact treatment you receive can be identified. Procedures for each visit are outlined below.

<u>Screening Visit 1 (-30 to -1 days)</u>
During the screening phase, you will be screened for your eligibility to participate in the study. Your medical history will be reviewed, and you will be asked about all medications you are currently taking. You will also complete standard MS measures: Expanded Disability Status Scale (EDSS), the 9-hole peg test (9HP, arm and hand function), and the Brief Repeatable Battery (BRB), a collection of cognitive tests which includes the Paced Auditory Serial Addition Test (PASAT; attention and processing speed), the Selective Reminding Test (SRT, a test of verbal learning and recall), the 10/36 Spatial Recall Test (10/36, spatial learning and recall), the Symbol Digit Modalities Test (SDMT, attention and processing speed), the PASAT, and Word List Generation task (WLG, listing words based on a category or initial letter). A blood sample (approximately 1 teaspoon) will be taken from a vein in your arm for standard safety lab tests to monitor your blood sugar, liver function, electrolytes, and kidney function.

You will also have a bone mineral density (DEXA) test done on your hips and spine. For this test, you will lie on an imaging table. After you are positioned as necessary for the scan, a scan bar will pass over your body. A beam of very low dose x-rays will pass through your body and will be measured by a detector. It will take approximately 15 to 30 minutes.

Baseline Visit 2 (Month 0)
The baseline visit will occur between 1 to 30 days after the Screening Visit. This will be a very tiring and long study visit, possibly lasting 5-6 hours. If you take stimulant medications such as methylphenidate (Ritalin), dextroamphetamine (Adderall), modafinil (Provigil), you will be told to not take them before the visit. You may bring them with you to take after the study procedures are done. You should also bring along any assistive walking device that you use.

At this visit, your blood pressure and weight will be measured. Several standard MS evaluations will be done, including the 6-minute walk test (6MWT), timed 25-foot walk (T25FW), 9 HPT, the BRB and Low Contrast Visual Acuity (LCVA – done 3 times, once for each eye and once with both eyes).

You will have an eye exam called Optical Coherence Tomography (OCT), which measures the thickness of the retinal nerve fiber layer in your eyes. You will have an OCT done on both eyes. For this procedure, you will be seated in front of the OCT machine and rest your head on a support to keep it still. The equipment will then scan your eye without touching it. If it is necessary to dilate your eyes for this test, you may be excluded from the OCT portion of the study, unless it is able to be scheduled after the other visit procedures have been completed or on a different day (within 2 weeks of the study visit).

If you meet the study entry criteria, you will be randomized at this visit to begin injections with either ACTH or placebo. The study nurse will train you and/or your caregiver how to give the injection. The study staff will call you every month to remind you which 3 days to take your study medication. You will be dispensed study drug and study drug logs to take home. You will be asked to complete the logs by writing down what time you do the injections and any side effects you may notice. You will be asked to bring empty drug vials and completed study drug logs with you to your next visit.

Visits 3, 6 and 8 (Months 3, 18, and 30)
At these visits, your blood pressure and weight will be measured, your skin will be examined and you will be checked for any swelling, which is a possible side effect of the study drug. You will be asked about any side effects you've had and the medications you are taking. You will return your empty drug vials and study drug logs, and will be dispensed drug logs and enough vials to last until your next study visit. The study staff will call you each month to remind you which 3 days to take your study medication.

At the study doctor's discretion, Visit 3 (Month 3) may be done over the telephone if traveling to the study site is a hardship for you, and if you have had previous experience with taking subcutaneous medications.

Visit 4 (Month 6)
The procedures for Visit 4 are the same as Visit 3, with the addition of a blood draw (1 teaspoon) for standard safety labs. You will return your empty drug vials and study drug logs, and will be dispensed drug logs and enough vials to last until your next study visit. The study staff will call you each month to remind you which 3 days to take your study medication.

Visits 5, 7 and 9 (Months 12, 24 and 36)
These 3 visits will be the same as the baseline visit; they will be very tiring and long study visits, possibly lasting 5-6 hours. If you take stimulants, you will be told to not take them before the visit. You may bring them with you to take after the study procedures are done. You should also bring along any assistive walking device that you use.

You will return your empty drug vials and study drug logs, and will be dispensed drug logs and enough vials to last until your next study visit. The study staff will call you each month to remind you which 3 days to take your study medication.

Potential Relapses
If you feel you are experiencing an MS relapse (new or worsening neurological symptoms lasting more than 24 hours, you should contact your treating neurologist (who may or may not be associated with this study). Please also notify the study nurse at 612.624.8431. If you are seen by your neurologist for a possible relapse, we will ask

you to allow us to obtain copies of your neurologist's clinic notes and/or other medical records related to the relapse (e.g., MRI scan). The cost for visits to your treating neurologist and for any procedures or treatments s/he prescribes will be charged in the usual manner, to you or your insurance company.

Unscheduled Visits

If you have any new symptoms that are of concern to you, you are encouraged to contact the study nurse at 612.624.8431. If the symptom is potentially serious and could possibly be related to the study drug, you will be asked to come to the CNRU for an unscheduled visit. The procedures at this visit will be the same as those done for Visit 3.

Study Schedule

	V1 Screen --30 days to -1 day	**V2** Baseline M0	**V3** M3	**V4** M6	**V5** M12	**V6** M18	**V7** M24	**V8** M30	**V9** M36	Unsched Visit
Informed Consent	X									
Inclusion/Exclusion	X									
Injection Training		X								
Blood Pressure		X	X	X	X	X	X	X	X	X
Weight		X	X	X	X	X	X	X	X	X
Safety Lab Tests	X			X	X		X		X	
Skin & Edema Assessment		X	X	X	X	X	X	X	X	X
OCT		X			X		X		X	
LCVA		X			X		X		X	
EDSS	X				X		X		X	
Timed 25-Ft Walk		X			X		X		X	
9-Hole Peg Test	X	X			X		X		X	
PASAT (apart from BRB-N)	X									
6 Minute Walk Test		X			X		X		X	
MS Walking Scale - 12		X			X		X		X	
Fatigue Severity Scale (FSS)		X			X		X		X	
Hauser Ambulation Index		X			X		X		X	
Brief Repeatable Battery	X	X			X		X		X	
DEXA Scans	X				X		X		X	
Randomization		X								
Symptom Questionnaire		X	X	X	X	X	X	X	X	X
Concomitant Medications		X	X	X	X	X	X	X	X	X
Adverse Events			X	X	X	X	X	X	X	X
Dispense Study Drug		X	X	X	X	X	X	X		
Return Drug Vials and Logs			X	X	X	X	X	X	X	

Risks of Study Participation
Four of the study visits (Baseline, M12, M24, and M36) will be very long and may be physically difficult. For instance, several of the MS evaluations which measure your walking ability may make you feel tired or exhausted. The 6MWT requires you to walk as far as you can in six minutes, while the EDSS requires you to walk for 500 meters (about 5 blocks) or until you need to stop. If you use stimulant medications, you will not be allowed to take your stimulants before the visits, but you can bring them with you and can take them after the study visit.

Possible side effects of ACTH include:
- increased risk of getting an infection
- adrenal insufficiency (which may include symptoms of weakness, skin color changes, weight loss, low blood pressure, and abdominal pain)
- fluid retention
- congestive heart failure
- high blood pressure
- low potassium levels
- high blood sugar
- muscle weakness
- loss of muscle
- loss of bone mass and increased fracture risk
- stomach ulcer
- stomach bleeding
- pancreas swelling
- stomach enlargement
- increased risk of gastrointestinal perforation (a hole forms all the way through the stomach, bowel or small intestine)
- poor wound healing
- thin fragile skin
- bruising
- increased sweating
- dizziness
- headache
- menstrual irregularities
- eye disorders (e.g., blurred vision or seeing double), cataracts (clouding of lens), glaucoma (damage to the eye's optic nerve which can lead to permanent vision loss)
- allergies, allergic or sensitivity reactions
- psychiatric side effects such as euphoria (an extreme high or "up" feeling), insomnia (difficulty sleeping), irritability, mood swings, personality changes, visual and auditory hallucinations (seeing or hearing things that are not there), confusion, and severe depression. If you experience any of these side effects, contact the study doctor immediately.

Because of the increased risk of infections, you should not receive live or live attenuated vaccines while you are in the study.

You may also experience injection site reactions, which include swelling, itching, redness and pain at the injection site.

ACTH and Pregnancy: Women who are pregnant, planning to become pregnant, or breastfeeding should not participate in this study, as ACTH could have negative effects on the fetus/baby.

Placebo: You will have a 50% chance of receiving placebo instead of active study drug. However, you will still be allowed to take any FDA-approved treatment that you were using provided you started it at least 3 months before Visit 2 (Baseline).

DEXA Scan: As part of this study, you will undergo one DEXA scan per year. This procedure involves exposure to ionizing radiation. The average amount of radiation that the average person would receive from this procedure is less than 0.3% of that received by natural sources of radiation by a Minnesota resident in one year (300mrem).

Blood Draw: The risks of drawing blood from a vein are minimal, and may include discomfort and slight bruising from the needle stick. Occasional dizziness, fainting, bleeding, or infection may occur. These risks will be minimized by clean and careful techniques.

OCT: There are no known risks associated with OCT. If your eyes need to be dilated, they may be sensitive to light following the procedure.

The study may involve risks which are currently unforeseeable. You will be informed of any new information that becomes available over the course of the study that may change your willingness to participate.

Benefits of Study Participation
There is no guarantee that you will receive any benefit from your participation in this study. Your condition may improve, worsen, or remain the same. The information obtained from this study may aid in the development of better treatments for progressive MS, which may improve the quality and/or prolong the lives of future patients.

Study Termination
Your participation in this study could be ended should any of the following occur:

- You decide to discontinue treatment
- You do not follow the directions of the study team
- The study doctor decides the study is not in your best interest
- You become pregnant or intend to become pregnant
- The blinding is broken (if the study doctor has to find out whether you are receiving ACTH or placebo in order to treat a side effect or for any other reason)

Regardless of the duration of your participation in the trial, upon termination you will be asked to return all unused ACTH/placebo to the CNRU. If you have been taking ACTH/placebo for a year or more, and you decide to withdraw from the study, we will ask you to continue to come in for the remaining annual study visits (Visit 7, Month 24, and Visit 9, Month 36), even though you will no longer be taking the study drug. If you have been taking ACTH/placebo for less than a year, we will ask you to participate in annual phone calls (Months 12 and 24), and to return to the site for the Month 36 study visit. You do not have to agree to return for these visits.

Alternatives to Study Participation
You do not have to be in this study to be treated for your condition. You may wish to discuss your treatment options with your doctor before you decide to participate. There are currently no FDA-approved drugs for the treatment of PPMS. Mitoxantrone is FDA-approved for SPMS and PRMS. Certain patients with SPMS and PRMS continue to experience intermittent MS relapses ("attacks"), and in those cases MS medications such as interferon beta, glatiramer actetate, natalizumab, fingolimod, teriflunomide and dimethyl fumarate may be considered.

Study Costs/Compensation
You will not be compensated for your participation in this study. All study procedures, study drug (ACTH or placebo), and parking for your study visits will be provided at no cost to you.

If you experience an MS relapse during the study, you or your insurance carrier will be responsible for the cost of any medications used to treat the relapse.

Research Related Injury
In the event that this research activity results in an injury, treatment will be available, including first aid, emergency treatment and follow-up care as needed. Care for such injuries will be billed in the ordinary manner, to you or your insurance company. If you think that you have suffered a research related injury, let the study physician know right away.

Confidentiality
The records of this study will be kept private. In any publications or presentations, we will not include any information that will make it possible to identify you as a subject. Your record for the study, however, may be reviewed by representatives of the study funder, Mallinckrodt Pharmaceuticals, and by departments at the University with appropriate regulatory oversight. A note indicating that you are participating in this study will be added to your medical records. To these extents, confidentiality is not absolute.

A description of this clinical trial will be available on http://www.ClinicalTrials.gov, as required by US 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 website at any time.

Protected Health Information (PHI)
We are committed to respecting your privacy and keeping your personal information confidential. When choosing to take part in this study, you are giving us permission to use your personal health information that includes health information in your medical records and information that can identify you. For example, personal health information may include your name, address, phone number or social security number. Those persons who get your health information may not be required by Federal privacy laws (such as the Privacy Rule or what you may know as "HIPAA") to protect it. Some of those persons may be able to share your information with others without your separate permission. Please read the separate HIPAA Authorization form that we have provided and discussed.

The results of this study may also be used for teaching, publications, or for presentation at scientific meetings.

Voluntary Nature of the Study
Participation in this study is voluntary. Your decision whether or not to participate will not affect your current or future relations with the University or the University of Minnesota Medical Center, Fairview. If you decide to participate, you are free to withdraw at any time without affecting those relationships.

Contacts and Questions
If you have questions about research appointments, the study, research results, or other concerns contact the researchers. The researcher conducting this study is Adam Carpenter, M.D. You may ask any questions you have now, or if you have questions later, you may contact him at 612.624.6145. You may also reach the study coordinator at 612.624.8431.

This research has been reviewed and approved by an Institutional Review Board (IRB) within the Human Research Protection Program (HRPP). To share feedback privately about your research experience, call the Research Participants' Advocate Line: 612.625.1650 (Toll Free: 1.888.224.8636) or go to z.umn.edu/participants. You are encouraged to contact the HRPP if:

- Your questions, concerns, or complaints are not being answered by the research team.
- You cannot reach the research team.
- You want to talk to someone besides the research team.
- You have questions about your rights as a research participant.
- You want to get information or provide input about this research.

The University of Minnesota HRPP may ask you to complete a survey about your experience as a research participant. You do not have to complete the survey if you do not want to. If you do choose to complete the survey, your responses will be anonymous. If you are not asked to complete a survey, but you would like to share feedback, please contact the study team or the University of Minnesota HRPP).

You will be given a copy of this form to keep for your records.

Statement of Consent
I have read the above information. I have asked questions and have received answers. I consent to participate in the study.

_____	_____	_____
Participant's Name (Print)	Participant's Signature	Date
_____	_____	_____
Name of Person Obtaining Consent	Signature of Person Obtaining Consent	Date