IRB #: 14074-448
(Assigned by IRB Office)

Approved
2/9/17
Cleveland VAMC
Institutional Review Board

CPA #: 7377
(Assigned by IRB Office)

***Form Directions**: Form is protected (user has limited access to the fill-in fields). Use the tab key or mouse to navigate the fill-in fields. Formatting is limited in the text fields (no bulleted lists, numbering, etc). In the event that the user is unable to navigate through the protected document or would like to format a document, the user can disable the "protected" feature (select "Review" then "Restrict Ending" then "Stop Protection"). Please do not delete or modify questions..*

Louis Stokes Cleveland Department of Veterans Affairs Medical Center Research Plan

Please contact the IRB office if you have any questions at (216) 791-3800 ext. 4658.

☐ **Request for Expedited IRB Review Form attached**

Human Subject Research: Human subject research means research involving interaction or intervention with living human beings or access to identifiable private information of living human beings.

Research Plan: The information requested in the Research Plan is designed to provide the IRB with the necessary information such that it can make the federally required determinations codified at 38 CFR Part 16, 21 CFR Parts 50, 54, & 56, and 45 CFR Part 46

The **Research Plan** is to be written so that the non-scientist/non-medical members of the IRB can understand the research proposed. Define all abbreviations and terms that are not part of common language.

Version Date: This should be updated subsequently with every modification to any part of the Research Plan. Any modification to this document, no matter how minor, must be reviewed and approved by the IRB prior to implementation. The Research Plan will be stamped with the date of IRB approval

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Section 1 – General Information

1. **Version Date:** 01/2017

2. **Title of Project:** Study and Treatment of Visual Dysfunction and Motor Fatigue in Multiple Sclerosis

3. **Principal Investigator (PI)** *(name & degrees)*: Alessandro Serra, MD, PhD

   E-mail: alessandro.serra@va.gov

   Pager Number/Cell Phone Number: University Hospitals pager 37194/4404655396

4. **Research Contact/Research Coordinator** *(name, degrees)*: **Jessica McCabe, M.P.T.**

   E-mail: jmccabe@fescenter.org

   Pager Number/Cell Phone Number: VA ext 3830

Section 2 – Research Sites and Sponsor

5. Please list all Research Sites in addition to Louis Stokes Cleveland DVA Medical Center (LSCDVAMC); N/A

International studies when the PI is the Lead Investigator list the countries:

a. When study procedures including analysis of identifiable samples or data involving LSCDVAMC enrolled subjects will be conducted at any site other than the LSCDVAMC please provide the following:

Name and contact information for the site:

Describe the plan for communicating protocol amendments, reports of serious adverse events, reports of unanticipated problems involving risks to subjects or others, interim reports, and DSMB reports to external sites.

*** When the LSCDVAMC is considered the coordinating center and the PI the lead investigator on cooperative research or a multi-center trial contact AO/Research Holly.Henry@va.gov.**

6. Sponsor or other Support *(list industry sponsor, government support, etc.)*:

CAREER DEVELOPMENT AWARD, Department of Veterans Affairs, REHABILITATION RESEARCH & DEVELOPMENT. Award Number I01BX007080

Section 3 – Research Design and Procedures

7. Definitions- Provide a list of all abbreviations and specialized terms to be used in this document and their definitions:

Abbreviations / Specialized Terms *(Use the Enter key in this column to insert additional abbreviations and their definitions)*	**Definition**
LSCDVAMC	Louis Stokes Cleveland DVA Medical Center
MS	multiple sclerosis
INO	internuclear ophthalmoplegia
MLF	medial longitudinal fasciculus
GEN	gaze-evoked nystagmus
CNS	central nervous system

8. Provide a BRIEF SUMMARY of the background for this research. DO NOT CUT and PASTE paragraphs that do NOT summarize the background.

- *Include a critical evaluation of existing knowledge, and specifically identify the information gaps that your protocol is intended to fill.*

- *Refer to appropriate citations in the scientific literature and include your references at the end of this section.*
- *Include the rationale for conducting the research at the VA.*

The study of eye movements is regarded as a powerful tool to investigate brain control of basic as well as high cognitive functions. As the neural substrate for eye movements is well understood, eye movement disorders are useful for localizing a pathological process within the central nervous system (CNS), and their study in the neuroscience allowed better understanding of both physiological and pathological conditions. The reason for extensive use of eye movements as a scientific tool, largely resides in their accessibility to measurement and analysis, as well as relatively easy reproducibility for experimental modeling. The proposed research aims at applying basic aspects of the control of eye movements to investigate gaze abnormalities, in particular concerning the coordination (conjugacy) of horizontal fast movements (saccades). The research strategy will be to use a typical multiple sclerosis (MS) ocular motor abnormality as a simple model to study the common but poorly understood complaint of fatigue in MS. The overall approach to the research here proposed stems from the well known history of basic and clinical investigations in the field of ocular motility, that has provided over the years insights into brain functioning and has translated into numerous treatments for patients with visual disability. The Daroff-Dell'Osso Ocular Motility Laboratory at the Louis Stokes DVA Medical Center, where the study will be conducted, has been a major contributor to vestibular and eye movement research for the last 30 years. The Daroff-Dell'Osso laboratory is a state-of-the-art eye movement center with top class equipment to conduct research in the field.

9. Provide a BRIEF SUMMARY of the purpose and scientific rationale for this research. DO NOT CUT and PASTE paragraphs that do NOT summarize the purpose and scientific rationale.

- *State clearly, in terms a non-scientist/non-medical person can comprehend, what you expect to learn from the study and the specific hypothesis (es) to be tested.*
- *The objectives should be stated in such a way that the reader can determine the appropriateness of the study design.*

With this proposal we expect to learn about mechanisms of motor fatigue in MS and provide a neurophysiological model for it, using a known eye movement abnormality often found in MS. More in general, we aim at studying the impact certain eye movement disorders have on often under-recognized visual dysfunction in patients affected. We will also evaluate the effect of a pharmacological treatment for a certain eye movement disorder in MS patients. Evidence suggests that primary motor fatigue, a highly disabling symptom in MS patients, originates within the CNS but a neurophysiological model to explain its underlying mechanisms is still lacking. As a consequence, medical treatment for fatigue are generally unsatisfactory. Moreover, fatigue remains difficult to objectify in the clinical settings as its assessment solely relies on subjective reports through standard questionnaries filled by patients (symptomatic fatigue). With this project, we propose a characteristic eye movement abnormality of eye coordination, internuclear ophthalmoparesis (INO), as a simple and accessible model for primary motor fatigue in MS. INO results from demyelination of a specific white matter tract in the brainstem (the medial longitudinal fasciculus, MLF) and is clinical evident with slowing of the adducting eye (i.e., the eye moving towards the nose) during horizontal gaze shifts, while the abducting eye (i.e., the eye moving away from the nose) is normal. Preliminary results in a small MS group show that patients with INO exhibit changes in ocular conjugacy (i.e., they show ocular motor fatigue) during a 10-minute recording of their fast eye movements (saccadic fatigue test), but normal subjects do not. In this respect, our hypotheses are: 1) ocular motor fatigue can complicate INO and is associated with worse scores of symptomatic fatigue than INO without ocular motor fatigue; 2) ocular motor fatigue is due to deterioration of neural conduction of the signal

needed to generate a saccade along the demyelinated MLF, which might be representative of a major component of primary motor fatigue in MS. The second part of the project concerns testing the effects of dalfampridine (a potassium channel blocker that enhances neural conduction along demyelinated axons) on MS-related INO with or without associated ocular motor fatigue. Visual dysfunction in MS patients with INO is a major cause of disability but no medical therapy is available. Our preliminary results document improved binocular conjugacy in three MS patients taking dalfampridine. In this respect, our hypotheses are: 1) dalfampridine improves visual performance in MS patients with INO and counteracts ocular motor fatigue; 2) improvement of INO and ocular motor fatigue with dalfampridine diminishes visual disability and improves quality of life in MS.

10. Describe the means of analyzing the data and evaluating the results.

- *State the anticipated methods to be used for analysis and interpretation of the data.*
- *The methods must compliment the design of the study and the nature of the data which is being collected.*

This study investigates horizontal binocular conjugacy and ocular motor fatigue in MS patients with INO and the effects of treatment (dalfampridine) while eye movements are recorded during a 10-minute saccadic fatigue test. Patients will undergo clinical eye movement examination, visual performance assessment including reading acuity and speed, gait assessment, assessment of symptomatic fatigue, disability arising from visual dysfunction as well as quality of life, using available self-administered questionnaires and scales, and eye movement recording, before and after treatment. The treatment portion of the study will be conducted following a randomized, placebo-controlled, double-blind, crossover trial design, which will include a period of wash out of at least two weeks between treatment with dalfampridine and placebo. A minimum of 2 weeks is necessary to ensure wash out, however a washout period longer than 2 weeks will not confound the study results. There will be a total of 4 evaluations: at baseline, after washout, and after treatment with both dalfampridine and placebo. Subject participation will last an estimated 10-14 weeks. We anticipate most subjects will participate for 10 weeks, however due to unforseen circumstances a subject may be unable to keep a scheduled appointment lengthening the overall time of their participation. In order to test our hypotheses, we use the following outcome measures, at time of each evaluation. A. Eye movement assessment: changes in binocular horizontal conjugacy at baseline and following the saccadic fatigue test using 1) abducting/adducting eye ratio for saccadic peak velocity (pulse size ratio); 2) time difference in occurrence of peak acceleration in the adducting vs. the abducting eye (pulse time delay). These measures of conjugacy of horizontal saccades are applied to data collected continuously throughout the fatigue test. B. Symptomatic fatigue assessment using 1) Fatigue Severity Scale (FSS); 2) Modified Fatigue Impact Scale (MFIS); C. Visual function assessment using 1) MNREAD acuity charts for reading acuity and speed; 2) King-Devick test for saccades performance; D. Gait assessment using 1) 25-foot Walk Test; 2) 6-minute Walk Test. E. Visual disability and quality of life assessment using 1) NEI-VFQ-25 and NOS; 2) MS Quality of Life Inventory. Standard statistical measures, such as paired dependent t-test, will be employed to determine significance of our results.

11. Provide a BRIEF DESCRIPTION of how the estimated number of study subjects needed for this research was determined

- *If this is a quantitative study provide the method of determining sample size estimates.*
- *If multiple studies are planned provide a power analysis or justification for each one.*

To determine the number of subjects needed for this study, we conducted a power analysis based on our preliminary data of increase in pulse size ratio and pulse time delay after the 10-minute fatigue test in two different sample populations of MS patients with INO. Based on a large effect size of 0.93, we found that we will need a sample size of 9 patients to reach a power of 0.80 (alpha 0.05) for the first outcome measure (pulse size ratio). Based on a moderately large effect size of 0.63, we found that we will need a sample size of 17 patients to reach a power of 0.80 (alpha 0.05) for the second outcome measure (pulse time delay). Because only one out of three patients showed clinically significant changes of pulse size ratio and pulse time delay after dalfampridine, while changes were subclinical in the other two patients, we were not able to provide a power analysis for the expected effects of dalfampridine in our trial. However, we found that for a clinically meaningful effect size of 0.5, with alpha of 0.05, we will need a sample size of 27 patients to yield a power of 0.85 [Norman et al., 2000]. Thus we aim at recruiting, studying and treating 30 patients.

12. The research involves the following procedures conducted by and for what purpose:

PROCEDURE	PERFORMED BY:		PROCEDURE IS:	
	Research Staff	LSCDVAMC Clinical or Support Staff	Standard of Care*	For Research Purposes Only**
Audiotaping / Videotaping *Attach VA Form 10-3203* **REQUIRED ONLY FOR IN-PATIENT AND OUT-PATIENT SUBJECTS**	☒	☐	☐	☒
Biopsy	☐	☐	☐	☐
Blood collection	☐	☒	☐	☒
Chart review – prospective	☒	☐	☐	☒
Chart review – retrospective	☒	☐	☐	☒
Review of existing data (ex: registry, Database , etc.)	☒	☐	☐	☒
X-ray or Ionizing radiation exposure	☐	☐	☐	☐
Clinical Tests	☒	☐	☐	☒
Device implantation	☐	☐	☐	☐
Drug administration	☐	☒	☐	☒
EEG, EKG , ECG…etc	☐	☐	☐	☐
Gene therapy, Genetic analysis	☐	☐	☐	☐

PROCEDURE	PERFORMED BY:		PROCEDURE IS:	
	Research Staff	LSCDVAMC Clinical or Support Staff	Standard of Care*	For Research Purposes Only**
Pregnancy/Breastfeeding Screening	☐	☒	☐	☒
Interview, Questionnaire, Diary, Survey *(please attach)*	☒	☐	☐	☒
Stool collection, Urine collection, or any Non-surgical Specimen collection	☐	☐	☐	☐
Surgical procedure or Specimen removal during surgery	☐	☐	☐	☐
Tissue banking *(complete Section 12)*	☐	☐	☐	☐
Use of pre-existing tissues/specimens	☐	☐	☐	☐
Other *(list)*: Eye Movement Recording	☒	☐	☐	☒

- **Standard of care procedures are procedures performed in the course of normal medical care.*
- ***Research Procedures are performed for the purposes of this research alone.*

13. Please describe the research design and all study related procedures.

- *Describe **ALL PROCEDURES ASSOCIATED WITH THIS RESEARCH**. This includes standard of care and research procedures.*
- *For complex studies please include diagrams and tables. Be sure to describe when each procedure will be performed. Be sure to provide information for **each cohort, including normal controls**).*

Patients cohorts (n=30).

Enrollment. Dr. Serra will be responsible for enrolling all patients for the study, whether he is the primary neurologist caring for the patients or whether they are being referred to him for possible enrollment in the study.

All patients will undergo neurological evaluation (medical history, clinical neurological examination, including eye movements exam, and blood work for renal function panel) prior to selection to establish whether or not they meet the study inclusion citeria. Possible female participants will also undergo a urine pregnancy test. Dr Serra will evaluate all patients as above.

Randomization and masking. Patients will be randomized to study drug or placebo for the first 4 weeks of treatment then, after a wash-out period of at least 2 weeks, they will cross-over to placebo and study drug respectively for another 4 weeks of treatment. Randomization process will be carried out by a VA research pharmacist. The patient, the PI, and all personnel and investigators involved in the study will be masked to treatment assignment. To avoid the possibility of a patient running out of the study drug/placebo at the time of the

2nd or 4th visit, for example in case of visit cancellation due to unforeseeable circumstances, the study drug/placebo will be sent out for 5 weeks. However, every effort will be made to schedule patients as close as possible to the 4-week mark for the 2nd and 4th visit. Additionally, all unused study medications will be returned by the subject to the laboratory at the 2nd and 4th visits.

Procedures to be performed at Evaluation 1 ,2 ,3 ,4.

Video tape of subjects' eye movements.

Eye Movement Recording. Eye movements will be recorded using the EyeLink II system, (SR Research Ltd.). Subjects will sit in a 110-ft-lb vestibular chair (CNC Engineering), with head restrained, during all the experimental paradigms, and will follow a visual stimulus (a red laser spot) projected onto tangent screen. The EyeLink signal from each eye will be calibrated. We will obtain a baseline monocular and binocular viewing recording of eye movements then will perform the 10-minute saccadic fatigue test as previously described [Matta et al, 2009]. Patients will make horizontal saccades in response to 20-degree jumps, at 0.5 Hz across the midline (i.e., 1 saccade per second), of the visual target (laser spot).

At evaluations 2 and 4, patients will hold the am dose (dalfampridine or placebo), will undergo baseline eye movement recording, then will be recorded again 3 hours after taking their dose in the same session.

Visual function assessment using MNREAD acuity charts for reading acuity and speed and the King-Devick test for saccades performance. Dr Serra will carry out these assessments.

Symptomatic fatigue assessment using self-administered questionnaires: the Fatigue Severity Scale (FSS) and the Modified Fatigue Impact Scale (MFIS).

Gait assessment using the 25-foot Walk Test and the 6-minute Walk Test. Dr Serra will carry out these assessments.

Visual disability and quality of life assessment using the following self-administered scales: NEI-VFQ-25 and NOS; and the MS Quality of Life Inventory.

Renal function panel (serum) at baseline, to be repeated after 4 weeks and at the end of the trial. Phlebotomy will be performed by a lab technician in the blood work laboratory located in the first floor of the LSDVAMC.

Normal controls cohort (n=20).

Enrollment. Dr. Serra will be responsible for enrolling all age-matched normal controls for the study, including possibly residents, house staff and employees of the LSDVAMC and Case.

All controls will undergo clinical evaluation of vision and eye movements to confirm they have normal visual and ocular motor functions.

Eye Movement Recording (one session only). Eye movements will be recorded using the EyeLink II system, (SR Research Ltd.). Normal controls will sit in a 110-ft-lb vestibular chair (CNC Engineering), with head restrained, during all the experimental paradigms, and will follow a visual stimulus (a red laser spot) projected onto tangent screen. The EyeLink signal from each eye will be calibrated. We will obtain a baseline monocular and binocular viewing recording of eye movements then will perform the 10-minute saccadic fatigue test as previously described [Matta et al, 2009]. Normal controls will make horizontal saccades in response to 20-degree jumps, at 0.5 Hz across the midline (i.e., 1 saccade per second), of the visual target (laser spot).

The table below summarizes the randomized, placebo-controlled, double-blind, crossover trial design, which will include a period of wash-out of at least two weeks between treatment with dalfampridine and placebo. In the event the washout period lasts longer than 2 weeks or a subject has difficulty keeping one of the study visits and needs to reschedule, subject participation would be greater than 10 weeks (estimated 10-14 weeks of participation).

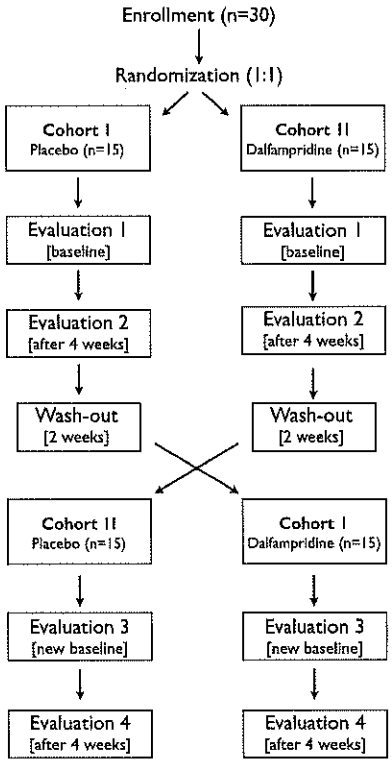

Table. Flow diagram summarizing study design. Following enrollment and randomization subjects will undergo a total of 4 evaluations, each one consiting in: eye movement recording, symptomatic fatigue assessment, visual function assessment, gait assessment, visual disability and quality of life assessment. Renal function panel (serum) will be performed at baseline, to be repeated after 4 weeks and at the end of the trial. See text for details.

14. Will the research involve the following?

☐ **N/A** **Chart/Data Review**

Placebo Group	☐ **No**	☒ **Yes** *(describe)*: double binded pacebo-controlled crossover trial of dalfampridine effects on INO and ocular motor fatigue in MS
Other Control Group	☐ **No**	☒ **Yes** *(describe)*: age matched for eye movement recording outcomes
Randomization	☐ **No**	☒ **Yes** *(describe)*: double binded pacebo-controlled crossover trial of dalfampridine effects on INO and ocular motor fatigue in MS

Deception ☒ **No** ☐ **Yes** *(describe)*:

15. Does the research involve the use and/or disclosure of Individually Identifiable Health Information in any form or medium?

☐ **No** ☒ **Yes** **If yes, complete the required HIPAA Waiver/Authorization forms.**

16. Does the study include the administration of a study agent that does not require FDA approval and does not require an IND (e.g. vitamins, food supplements, isotope tracers, alternative medicines, etc.)?

☒ **No** ☐ **Yes** *-provide a detailed description of the procedures used to assure patient safety:*

17. Will radioactive material be administered or will subjects be exposed to ionizing radiation?

- *Ex. Radiographic equipment, fluoroscopic equipment, and CT scanners, etc.*

☒ **No** ☐ **Yes**

18. In your judgment, could the objectives of the research be met in a way that presents less risk to subjects?

☒ **No** ☐ **Yes** *please explain*:

Section 4 – Subject Selection, Recruitment, and Vulnerable Populations

19. Anticipated duration of entire study reported in years: 3

20. Estimated number of subjects to be studied at the LSCDVAMC or charts/records to be reviewed.

- *Provide answers for **each cohort** including normal controls; (patients, family members, treating physicians,)*:

Patients: 30. Normal controls: 20.

21. Estimated number of subjects to be studied or charts/records to be reviewed at all sites

- *Provide answers for **each cohort** including normal controls; (patients, family members, treating physicians,)*

N/A SINGLE SITE ☒

22. Duration of individual subject participation

*Provide answers for **each cohort** including normal controls; (patients, family members, treating physicians,).* Patients: estimated 10-14 weeks. Normal controls: one day

Chart/record review ☐ **N/A**

23. Age range of subjects

- *provide answers for **each cohort**, including normal controls*:

☐ **Adults 18 years or greater**

☒ **Specific age range** (list age range): 18-65

☐ **Children –waiver from VACO:** ☐ **attached** ☐ **pending- *provide submission date:***

***Contact AO/Research holly.henry@va.gov for guidance..*

24. Which of the following will be recruited or reviewed for this study *(check all that apply)*?

☒ **Veteran Inpatients**

☒ **Veteran Outpatients**

☐ **Veteran Families**

☒ ***Normal volunteers**

☒ **Men**

☒ **Women**

☒ ***Non-Veterans; Provide justification To reach the target enrollment number of 30 patients to study and treat in 3 years. At the LSDVAMC we follow a population of about 300 MS patients. While INO is fairly common in MS, only cases of mild/moderate INO, but not severe, will be enrolled in our study. Thus, recruitment of Non-Veterans may be necessary to reach the required number of patients for the study. Subjects may be recruited from Dr. Serra's practice at University Hospitals, and through referrals from colleagues at University Hospitals, Cleveland Clinic and community practices. However, every effort will be made to include as many Veterans as possible in our study.**

*According to VHA Handbook 1605.04 Notice of Privacy Practices VHA must provide a copy of its VHA Notice of Privacy Practices to all non-Veteran patients (e.g., active duty personnel or those seeking care in humanitarian circumstances) receiving care or treatment at a VHA health care facility or non-Veteran research subjects enrolled in an approved VHA research study with clinical trials. VA Form 10-0483 Acknowledgement of the Notice of Privacy Practices should be signed by the non-Veteran research subject at the time of consent and given a copy of the Notice of Privacy Practices. Once the Acknowledgement Form is signed please send a copy to the Privacy Officer. If additional information is needed please contact your Facility Privacy Officers Joseph Picklo or Tomica Jefferson joseph.picklo@va.gov / phone 8214102 tomica.jefferson@va.gov / phone 8214101.

25. Which vulnerable population(s) will be TARGETED for recruitment in this study:

- *Indicate only those populations that are specifically targeted for the research described in this document.*
- ***It is not necessary to check any box if, for example, your study will include a full range of subjects, some of whom may be elderly or subjects who might incidentally be employees.***

☐ **N/A Chart Review** (*proceed to Item 30*)

☐ **NONE** (*proceed to Item 26)*

☒ **Medical students, house staff, or Employees of the VAMC or Case**

☐ **Pregnant Women OR Women who are Breastfeeding, Human Fetuses, or Neonates**

☐ **Children – Complete Section 14 "Children as Research Subjects"**

☐ **Prisoners (The LSCDVAMC does not conduct research involving prisoners)**

☐ **Targeting Persons over Age 65**

☐ **Persons with Acute/Severe Mental/Physical Disabilities** *(describe)*:

☐ **Persons with Cognitive, Social, Economic, or Educational Disadvantages** *(describe)*:

☐ **Others** *(describe)*:

a. Provide the Scientific and Ethical reasons for Targeting these vulnerable populations in the research:

We need age-matched control subjects, and seek volunteers from the faculty and staff of Case Western Reserve University.

b. What additional safeguards or provisions will be used to protect the rights and welfare of the identified targeted vulnerable subjects?

☐ **Surrogate consent**

☐ **Subject assent**

☐ **Use of a consent or Medical monitor**

☐ **Use of a waiting period**

☐ **A patient advocate will participate in the informed consent process**

☐ **Key elements of informed consent will be presented orally**

☐ **No supervisor or rater will be involved in obtaining consent**

☒ **Other - Describe Additional safeguards you plan to use:** Dr. Serra will personally make it clear that they are under no obligation to volunteer their time, and their refusal to do so will not affect their collegial relationship with him or have any other adverse effect. This will be a discussion based on respect for colleagues. We will not recruit students or other staff who are being supervised or evaluated by Dr. Serra, or who in any other way would feel obliged to serve as a subject.

c. Describe the procedures used to ensure that the subject's legally authorized representative is well informed regarding his/her role and obligation to protect persons with impaired decision making capacity:

N/A. We will not study patients who are unable to give informed consent.

26. Procedures for Recruiting Subjects -check all that apply and attach all recruitment materials:

☐ **Not Applicable**

☒ **Materials; Recruitment Letter, Posting on Bulletin Board, Brochure, Flyer, Post card, etc.**

☐ **Media; Internet Ads, Press Releases, Newspaper, Radio**

☒ **Investigator's Patient Population**

☒ **Physician Referral**

☐ **Letters to Physicians/Clinicians**

☒ **Other** *(describe)*: advertising in the National MS Society local newsletter

27. Will VA computer systems be used to identify potential subjects?

- *e.g. VISTA, CPRS, Pharmacy Databases, other clinical databases, etc,*

☐ **No** ☒ **Yes- Describe how the computer will be used to identify patients. List all systems used and all information to be collected:** VA computers will be used to define if VA subjects, whether they are patients already followed by Dr. Serra or being referred to him by a VA colleague, meet inclusion criteria for the study. For this purpose, Dr. Serra will review patients' name, last 4 digits of SSN, charts in CPRS and patients' neuroimaging in VISTA.

28. Will subjects be identified and/or recruited in clinics and/or inpatient wards at the LSDCVAMC?

☐ No ☒ Yes- **explicitly describe your process for identifying and/or recruiting these patients:** *(address all cohorts):* Individuals evaluated in Neurology Monday afternoon and Tuesday morning outpatient clinics (Module H) or on the Neurology Inpatient Service (fifth floor) by Dr. Serra, who are suitable for inclusion in the study will be approached by Dr. Serra. Physicians at the medical center who identify patients suitable for the study will first ask the patient if they are interested in talking to Dr. Serra about the study; if they are, Dr. Serra will talk with them about the possibility of becoming a study patient.

29. In addition to the consent form will any other materials be given to the subject?

☐ **N/A Chart/data review**

☐ **No** ☒ **Yes- check all that apply and submit for IRB review:**

- ☐ **Letter**
- ☐ **Information Sheets**
- ☒ **Questionnaire, Survey, Diary**
- ☐ **Other** *(flyer, brochure, describe):*

30. Please list by bullet point inclusion/exclusion criteria for the study.

- *Entry criteria should be as detailed as necessary to define the subject population(s) under study and reduce confounding design. Include precise criteria for age, gender, and other relevant factors.*
- *List specific exclusion criteria which could interfere with the study design or place a subject at risk during the study.*
- *Provide answers for* ***each cohort****, including normal controls.*

Patients cohort.

Inclusion criteria:

- Diagnosis of MS of any course and duration

- Evidence of mild to moderate INO (slowing of the adducting eye) on physical examination of saccadic speed, whether INO is unilateral or bilateral, symmetrical or asymmetrical

- Medically stable conditions, ability to give informed consent and understand and cooperate with the testing

- Dalfampridine-naive as well as history of taking dalfampridine in the past, whether there was benefit in gait impairment or not, after a washout period of at least 2 weeks.

Exclusion Criteria:

- Lack of evidence of INO (slowing of the adducting eye) on physical examination of saccadic speed

- Severe INO (i.e., exotropia in primary gaze) on physical examination

- Medically unstable conditions, inability to give informed consent and/or understand and cooperate with the testing

- History of side effects from dalfampridine

- History of seizures

- Moderate or severe renal failure, assessed by clearance of creatinine

- Pregnancy.

Normal controls cohort.

Inclusion criteria:

- Age 18-65

- Healthy with normal visual and ocular motor function

☐ **N/A Chart/data review**

31. By role, (PI, Coordinator, etc.) who will assess for eligibility and how will this be accomplished?

Eligibility will be assessed by the PI, Dr. Serra, who will conduct formal neurological, neuro-ophthalmologic and neurotological clinical examinations. Then subjects will be selected based on the inclusion criteria specified above.

32. Are any subjects excluded on the basis of race, ethnic group, understanding of English, socioeconomic status, education, gender, or pregnancy?

- *Note: It is appropriate to indicate that you do not anticipate encountering potential subjects who do not speak English* ***based on the population to be studied***

☐ **No** ☒ **Yes** - *(provide justification)*: Non-English speaking individuals who cannot give informed consent will be exlcuded because they will be unable to follow the directions required to conduct the experiments. We will exclude individuals who are pregnant or likely to become pregnant because the study involves the use of a category C medication such as dalfampridine.

☐ **N/A Chart/data review**

33. Will subjects be reimbursed or paid an incentive for participating?

☐ **No (skip to item #35)** ☒ **Yes**

☐ **N/A Chart/data review (skip to item #38)**

34. How and when will they be paid?

☐ **Cash** ☒ **Check** ☐ **Other** -please explain:

☐ **Prorated** -provide schedule: ☒ **Fixed** -provide schedule Subjects will be paid $37.50 by check for each study session, which includes the eye movement recording (total four study sessions). They will receive the payment at the end of each session. If a subject completes all of the scheduled sessions, he/she will have received $150.00 total. Payment does not apply to healthy control.

35. Will subjects be responsible for any of the costs related to the research?

☒ **No** ☐ **Yes-** please explain:

36. Will treating physicians, clinicians, or researchers be compensated or paid an incentive for referring or enrolling subjects?

☒ **No** ☐ **Yes** -please explain:

37. Please describe steps you will take to ensure that subject selection is fair and equitable:

We will approach a full range of MS patients when we encounter them to see if they are interested in being a research subject. An effort will be made to include patients of different age, race, sex, etc. We will approach age-matched normal subjects to act as control subjects as the opportunities occur.

Section 5 – Risks and Benefits

38. Please list by bullet and describe the reasonably foreseeable physical, psychological, social, economic, and privacy risks, side effects, or discomforts associated with the research and their expected frequency and severity.

- *If this study is a retrospective chart review, or involves only the analysis of data, risk may still be present in the form of data security concerns.*

STUDY DRUG RISKS

Participation in this study may involve some risks related to the administration of dalfampridine (AMPYRA). This medication is commonly prescribed in clinical practice and its possible side effects are well known. AMPYRA is usually well tolerated. The most common adverse events (incidence ≥2% and at a rate greater than the placebo rate) for AMPYRA are urinary tract infection, insomnia, dizziness, headache, nausea, asthenia, back pain, balance disorder, multiple sclerosis relapse, paresthesia, nasopharyngitis, constipation, dyspepsia, and pharyngolaryngeal pain. AMPYRA can cause seizures; the risk of seizures increases with increasing AMPYRA dose. AMPYRA can cause anaphylaxis.

BLOOD WORK AND NEEDLE STICK RISKS

Renal function will be checked through standard blood work at baseline, after 4 weeks and at the end of the study. The insertion of the needle to draw blood is painful; however, this discomfort is brief. For most people, needle punctures to get blood samples do not cause any serious problems; however, they may cause bleeding, bruising, discomfort, infections, dizziness, or fainting.

STUDY PROTOCOL'S RISKS / DISCOMFORTS

Subjects might experience some discomfort when we record their eye movements as they will have to wear a helmet and their head will have to be stabilized using a chin rest. They will have to look at a stationary and moving visual target, and might be asked to rotate their

head from side to side or up and down. Also, following a target on the screen requires concentration and subjects might find this a bit challenging especially towards the end of the recordings.

Subjects will have to answer some questionnaires about quality of life, visual function and fatigue. Some of the questions may be upsetting, or they may feel uncomfortable answering them.

DATA SECURITY RISKS

As this study involves analysis of data and protected health information (PHI), concerns for data security exist.

***Certificate of Confidentiality:**

- Certificates of Confidentiality are issued by the National Institutes of Health (NIH) to protect identifiable research information from forced disclosure.
- They allow the investigator and others who have access to research records to refuse to disclose identifying information on research subjects in any civil, criminal, administrative, legislative, or other proceeding, whether at the federal, state, or local level.
- Certificates of Confidentiality may be granted for studies collecting information that, if disclosed, could have adverse consequences for subjects or damage their financial standing, employability, insurability, or reputation.
- By protecting researchers and institutions from being compelled to disclose information that would identify research subjects, Certificates of Confidentiality help achieve the research objectives and promote participation in studies by assuring confidentiality and privacy to subjects.
- **For more information, see http://grants1.nih.gov/grants/policy/coc/index.htm.**

39. Is this project principally concerned with the collection of sensitive information such as sexual attitudes, use of drugs or addictive products, and illegal conduct that would need to be protected against subpoena or forced disclosure in order to protect subjects?

☒ No

☐ Yes- will an application for a *Certificate of Confidentiality be submitted to the National Institute of Health upon IRB approval (or approval contingent on the issuance of such a certificate)?

☐ Yes ☐ **No provide a justification as to why a Certificate of Confidentiality will not be obtained:**

40. Describe all procedures that minimize risks, please include study and standard of care procedures:

We will not enroll subjects in which AMYRA is contraindicated: history of seizure, moderate or severe renal impairment, history of hypersensitivity to AMPYRA or similar compounds. To minimize possible side effects, subjects will be taking the FDA-recommended dose of AMPYRA (10 mg tablet twice daily), with doses taken approximately 12 hours apart and only taken whole. Subjects will be advised not to take double or extra doses if a dose is missed.

Since AMPYRA can cause side effects, especially seizures, in subjects with abnormal renal function, this will be checked through standard blood work at baseline, after 4 weeks and at the end of the study.

We will keep all eye movement recordings under 30 minutes to minimize possible discomfort.

If subjects do not wish to answer a question in a questionnaire, they may skip it and go to the next question.

To ensure confidentiality of patient's records, we will keep all records on a password-protected computer in Room BC 300c in the Daroff-Dell'Osso Ocular Motility Laboratory. This computer has an encryption firewall. Paper records will also be kept in a locked cabinet in Room BC 300c; the keys to the room and cabinet will be retained by Dr. Serra . Each patient will be assigned a number based on the hour and date of their study. The key to the numbers/patients will be stored in Dr. Serra's password-protected computer and in the memories of each patient and Dr. Serra's. At the end of the study, all data will be stored on a password-protected CD, kept in Dr. Serra's locked cabinet and will be retained indefinitely.

41. Describe alternative procedures or course of treatment, if any, which might be advantageous to the subject. State if no alternatives exist or if this is not a treatment study.

AMPYRA is potentially available to subjects outside of the research study with the FDA-approved indication for gait impairment. Because of the nature of this research the only alternative is to not participate in this study. Currently, there are no other approved treatment/drugs for the treatment of INO.

Minimal Risk: Minimal risk means that the risks of harm anticipated in the proposed research are not greater, considering probability and magnitude, than those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests.

42. Please give your overall risk classification for the research:

☐ **Minimal Risk**

☒ **Greater than Minimal Risk**

43. Will subjects receive any <u>direct</u> benefit from this research?

☒ **No** ☐ **Yes** -describe the direct benefits:

44. Please explain briefly why you consider the risks associated with the study to be reasonable in relation to its benefits?

Risks associated to the study are mostly related to the administration of the study drug, which is however FDA approved although for a different indication, and is overall well tolerated. The rest of the study, including eye movement recording, may cause some discomforts but poses no real risk of harm for the subjects. These risks are reasonable in relation to potential direct benefits for the patients and indirect benefits coming from a better understanding of the complex symptom of motor fatigue in MS.

Section 6 – Informed Consent

45. Type and number of Consent-

- *When more than one consent form is being used a descriptor MUST be in the header section describing the population and/or phase of the study:*

☒ **Written Informed Consent –number used in this study** one

☒ ***Oral Script/Letter/Information Sheet- number used in this study** one ***Submit Request for Consent Waiver Form-waiver of documentation of informed consent**

☐ **No informed consent at all in this study- Submit a Request for Consent Waiver Form-waiver of informed consent and proceed to item 53**

46. Will all adult subjects have the capacity to give informed consent?

☒ **Yes** ☐ **No- Describe range of impairment.**

- *Research involving more than minimal risk, capacity should be determined by a psychiatrist, clinical psychologist, or other qualified professional not otherwise involved in the research.*
- *Individuals who lack the capacity to consent may participate in research only if a legally authorized representative gives consent on their behalf.*

47. Will anyone other than the subject be authorized to provide consent or permission for the subject's involvement in the research?

- *e.g., parents, court ordered guardian, spouse, etc.*

☒ **No** ☐ **Yes** -please explain:

48. Describe <u>how</u> and <u>where</u> informed consent will be obtained:

The PI will explain the nature of the study to the patients and control subjects during recruitment in the clinic(s) or in-patient service. When the patient comes to be studied or is referred to discuss the opportunitity of participating in the study, in the Daroff-Dell'Osso Laboratory, BC300, Dr. Serra will go over the protocol, and the patient will have the opportunity to decline.

49. Will there be an opportunity for potential subject to take the consent form home to discuss participation and options with family members?

☒ **Yes** ☐ **No** - please explain:

50. List by role who will be obtaining informed consent from subjects or their legally authorized representatives:

- *ex. study coordinator, co-investigator, research nurse, research assistant, PI*

PI

51. Please describe how informed consent will be obtained from subjects who do not read or understand English;

- *identify any languages likely to be encountered, and attach a copy of a translated and authenticated informed consent document*
- *It is appropriate to indicate that you do not anticipate encountering potential subjects who do not speak English based on the population to be studied*

We will not recruit subjects who do not speak English.

52. Describe who *(by Role ex. PI, Coordinator, etc.)* **and how it will be determined that subjects and/or legally authorized representative understand the research and their rights.**

- *ex. question and answer, repeat back parts of the research, describe a procedure...etc*

By engaging the patient in an unhurried conversation, with ample time for them to ask questions and discuss the nature of the study described by the PI. In order to maintain the blinding of the study, subjects will be advised that the pill of AMPYRA they will be taking in the study may or may not look like the AMPYRA that is commercially available and that they may have taken in the past. Also, the subjects will be advised not to discuss the pill they are taking, its appearance, possible side effects they may be experiencing, with Dr. Serra or other people conducting the eye movement recording and the other assessments of this study. If experiencing any side effect or if they have questions about the pill they are taking, subjects can contact Dr. Mark Walker (contact info can be found in the consent form).

Section 7 – Privacy and Confidentiality

Privacy - refers to a person's desire to control the access of others to themselves. For example, persons may not want to be seen entering a place that might stigmatize them, such as a pregnancy counseling center that is clearly identified as such by signs on the front of the building. Privacy concerns people, whereas confidentiality concerns data. The research proposal should outline strategies to protect privacy including how the investigator will access information about potential subjects.

In developing strategies for the protection of subjects' privacy, consideration should be given to:

- Methods used to identify and contact potential subjects
- Settings in which an individual will be interacting with an investigator
- Appropriateness of all personnel present for research activities
- Methods used to obtain information about subjects and the nature of the requested information
- Information that is obtained about individuals other than the "target subjects," and whether such individuals meet the regulatory definition of "human subject" (e.g., a subject provides information about a family member for a survey)
- How to access the minimum amount of information necessary to complete the study

Confidentiality - methods used to ensure that information obtained by researchers about their subjects is not improperly divulged. Confidentiality refers to the researcher's agreement with the subject about how the subject's identifiable private information will be handled, managed, and disseminated. The research proposal should outline strategies to maintain confidentiality of identifiable data, including controls on storage, handling, and sharing of data. When appropriate, certificates of confidentiality could be used to maintain the confidentiality of identifiable data

When the IRB evaluates research proposals for strategies for maintaining confidentiality, where appropriate, consideration will be given as to whether:

- Methods to shield subjects' identity adequately protect subject privacy
- There is a long-range plan for protecting the confidentiality of research data, including a schedule for destruction of identifiers associated with the data
- The consent form and other information presented to potential research subjects adequately and clearly describe confidentiality risks.
- The informed consent process and the informed consent document, and if applicable the Authorization Form, clearly delineates who will have access to the subject's information and under what circumstances data may be shared (i.e., government agencies, sponsors).

53. Describe when and where subjects will provide their information. Include the nature of the information and who will receive and use the information. Document the provisions used to protect privacy interests of those subjects when gathering their information and data.

To ensure confidentiality of patient's records, we keep all records on a password-protected computer in Room BC 300c in the Daroff-Dell'Osso Ocular Motility Laboratory. This computer has an encryption firewall. Paper records will also be kept in a locked cabinet in Room BC 300c; the keys to the room and cabinet will be retained by Dr. Serra . Each patient will be assigned a number based on the hour and date of their study. The key to the numbers/patients will be stored in Dr. Serra's password-protected computer and in the memories of each patient and Dr. Serra's. At the end of the study, all data will be stored on a password-protected CD, kept in Dr. Serra's locked cabinet and will be retained indefinitely. All documents created during this research will be kept in their original form. All documents will not be destroyed.

54. Will researchers have access to identifiable private information about potential subjects <u>outside</u> of this research project? *Ex. PI is provider who has access to medical records for clinical care*

☐ **No** ☒ **Yes- please explain:**

Dr. Serra will be the primary neurologist for some of the subjects studied.

55. Will Researchers collect identifiable private information on anyone other than the subject?

- *Ex. family members, friends, colleagues, classmates...etc.*

☒ **No** ☐ **Yes -please explain:**

56. At the time data are transcribed or recorded for this study they are?

☐ **Fully identifiable- list identifiers to be collected:**

☒ **Coded with a unique identifier- describe the code:** Time/Date of collection

a. Who will have access to the key? Dr. Serra

b. Where is the key maintained? Two locking barriers must be in place between the coded data and the key. Room BC300c

☐ **De-identified-by Privacy Officer or Statistician.**

☐ **Other** *(describe)*:

57. How will electronic research data be secured while the study is active?

☐ **No electronic data will be stored**

☐ **VA encrypted laptop**

☒ **Encrypted VA device/media- describe: password-protected VA desktop computer**

☒ **VA network drive;**

☐ **M: drive; whose?**

☒ **S: drive**

☒ **Folder access password protected**

☐ **Other drive location** *(for example P: drive)*:

☐ **Folder access password protected**

58. How will hardcopy research data be secured while the study is active? Two locking barriers must be in place.

☐ **No hardcopy data will be stored**

☒ **Locked office and locked file cabinet**

☒ **Data coded by PI or study staff with a master list secured and kept separately**

☐ **Data de-identified by Privacy Officer or Statistician- (VA does not consider coded data to be de-identified)**

☐ **Other -specify:**

59. Provide the physical location including room number (and address if outside of this VA) where all electronic and hardcopy data will be stored: Wade Park Room BC 300c

60. Is identifiable information physically or electronically sent TO the LSCDVAMC from other institutions or locations?

☒ **No** ☐ **Yes** - contact Privacy Officer Joseph Picklo or Tomica Jefferson joseph.picklo@va.gov / phone 8214102 tomica.jefferson@va.gov / 8214101 or Information Security Officer Bruce Frankford bruce.frankford@va.gov / phone 821 1604 – prior to submitting to the Research Service.

****If yes complete the following:**

a. LSCDVAMC investigator will receive:

☐ **Hardcopy information or specimens**

☐ **Electronic information**

b. What are the procedures for transporting and/or transmitting identifiable information securely?

c. What will be the final disposition of the identifiable data transferred to the LSCDVAMC?

- **Record Control Schedule 10-1 indicates that all research records must be retained indefinitely**

61. Is identifiable information physically or electronically sent FROM the LSCDVAMC to other institutions or locations?

☒ **No** ☐ **Yes** contact Privacy Officer Joseph Picklo or Tomica Jefferson joseph.picklo@va.gov / phone 8214102 tomica.jefferson@va.gov / 8214101 or Information Security Officer Bruce Frankford bruce.frankford@va.gov / phone 821 1604 – prior to submitting to the Research Service

****If yes complete the following:**

a. The LSCDVAMC investigator will send:

☐ **Hardcopy information or specimens**

☐ **Electronic information**

b. What are the procedures for transporting and/or transmitting identifiable information securely?

c. What will be the final disposition of the identifiable data transferred offsite?

- **Record Control Schedule 10-1 indicates that all research records must be retained indefinitely**

62. Record Control Schedule 10-1 indicates all research records must be retained indefinitely. Please indicate where this information will be stored and the safe guards to protect it:

a. Electronic Safeguards:

☐ **No electronic data will be stored**

☐ **VA encrypted laptop**

☒ **Encrypted VA device/media- describe: password-protected VA desktop computer**

☒ **VA network drive;**

- ☐ **M: drive; whose?**
- ☒ **S: drive**
  - ☒ **Folder access password protected**
- ☐ **Other drive location** *(for example P: drive)*:
  - ☐ **Folder access password protected**

b. Hardcopy safeguards. Two locking barriers must be in place.

☐ **No hardcopy data will be stored**

☒ **Locked Office and Locked File Cabinet**

☒ **Coded by Study Staff**

☐ **De-identified by Privacy Officer or Statistician**

☐ **Other- Describe:**

Facility name, address, and room number where hardcopy or electronic data will be stored:
LSDVAMC, Room BC 300c, 10701 East Boulevard, Cleveland, Ohio, 44106

Section 8 – Data and Safety Monitoring –Greater than Minimal Risk Study

- For all research that is greater than minimal risk a Data and Safety Monitoring Plan must be developed.

- This is a plan to assure the research includes a system of appropriate oversight and monitoring of the conduct of the study to ensure the safety of subjects and the validity and integrity of the data.

***CHECK BOX IF THIS IS A MINIMAL RISK STUDY ☐ SKIP TO #65**

63. Safety monitoring for this greater than minimal risk project will include:

☐ **Data Safety Monitoring Board:**

☐ **Data Monitoring Committee**

☐ **Other**

- *Attach the plan or provide details including whether committee is independent from the study sponsor, how often it meets, whether written reports are available, etc*

The study involves a FDA-approved drug whose risks are well known. Dr. Serra will report any unexpected adverse events to the IRB.

64. Describe the plan for on-site data monitoring by the sponsor, contract research organization (CRO), or other independent body: N/A

- **Research Office must be notified of all on-site monitoring visits.*

65. Conditions that may result in removal of subjects from the research *(check all that apply)*:

☐ **Medical condition unchanged**
☒ **Medical condition worsened**
☒ **Serious adverse event**
☒ **Intolerable complications**
☒ **Pregnancy**
☒ **Investigator's clinical judgment**
☒ **Subject withdrawal**
☒ **Subject uncooperative or noncompliant**
☒ **Study closure by sponsor or FDA**
☒ **Refusal to suspend breast-feeding**
☐ **Other-describe:**
☐ **Not Applicable**

66. If a subject withdraws or is removed from the study, describe the potential risks of early withdrawal and the procedures in place to minimize these risks:

None

Section 9 – FDA-Regulated Drugs/Biologics

NOTE: If this research involves the use of <u>any</u> drugs or biologics, the study is subject to the Food and Drug Administration (FDA) regulations.

- **Documentation of FDA approval for the experimental use of these agents must be provided for review (industry sponsored protocol listing the IND number, letter from the FDA, letter from industry sponsor, or other document and/or communication verifying the IND for this study).**
- All drug/biologic products must be dispensed and tracked through the LSCDVAMC Research Pharmacy.
- An M.D. must be part of the Research Team for all studies that involve the use of a device or drugs.

- The LSCDVAMC Pharmacy and Therapeutics (P&T) Committee must approve: (1) Studies of investigational drugs (2) research involving an FDA-approved drug used in a non-approved manner, and (3) an FDA-approved drug, used as approved, when its use is part of a research protocol.
- **VA Form 10-9012 Investigational Drug Information Record** –must be completed for each drug being evaluated in a research study, regardless of IND status. In addition, the VA Form 10-9012 provides a listing of all authorized prescribers for the study drug(s).

67. Type of Product- check all that apply:

☐ **Not Applicable -No FDA-regulated drugs/biologics involved – Proceed to Section 10**

☒ **Drug**

☐ **Biologic or Other:**

68. Type of Trial *(check as applicable)*:

☐ **Phase I** ☐ **Phase II** ☐ **Phase III** ☐ **Phase IV** ☒ **NA**

Phase I Trials: Initial studies to determine the metabolism and pharmacologic actions of drugs in humans, the side effects associated with increasing doses, and to gain early evidence of effectiveness; may include healthy subjects and/or patients.
Phase II Trials: Controlled clinical studies conducted to evaluate the effectiveness of the drug for a particular indication or indications in patients with the disease or condition under study and to determine the common short-term side effects and risks.
Phase III Trials: Expanded controlled and uncontrolled trials after preliminary evidence suggesting effectiveness of the drug has been obtained, and are intended to gather additional information to evaluate the overall benefit-risk relationship of the drug and provide adequate basis for physician labeling.
Phase IV Trials: Post-marketing studies to delineate additional information including the drug's risks, benefits, and optimal use.

69. FDA Status of Drugs/Biologics –

*** For drugs, an IND may not be necessary if ALL seven of the following conditions are met:**

1. The drug being used in the research is lawfully marketed in the United States;
2. The research is not intended to be reported to FDA in support of a new indication for use or to support any other significant change in the labeling for the drug;
3. The research is not intended to support a significant change in the advertising for the product;
4. The research does not involve a route of administration or dosage level, use in a subject population, or other factor that significantly increases the risks (or decreases the acceptability of the risks) associated with the use of the drug product;
5. The research is conducted in compliance with the requirements for IRB review and informed consent (21 CFR parts 56 and 50, respectively);
6. The research is conducted in compliance with the requirements concerning the promotion and sale of drugs (21 CFR 312.7);
7. The research does not intend to invoke 21 CFR 50.24 (Exception from informed consent requirements for emergency research).

Provide the following information for <u>each</u> drug/biologic used in this study:

Trade and Generic Name	**Manufacturer**	FDA Approved	**Product use consistent with product labeling**	**IND Required***	**IND Number**	**IND Sponsor or Holder****
Ampyra (dalfampridine)	Acorda	yes	yes			

70. **When the PI holds the IND, complete the following:

i. The PI has reviewed the Guidance on Requirements of the Sponsor and the Investigator as Sponsor

☐ **Yes**

ii. As the PI, you will comply with the regulatory responsibilities of a sponsor

☐ **Yes**

71. Drug Information for each drug listed in the protocol -check as applicable

☒ **Approved Drugs**

☐ **Not Approved**

- **Attach VA Form 10-9012 Investigational Drug Information Record for each drug used in the protocol**
- **Attach Package Insert or PDR monograph – copy ready, 8.5 x 11 for each drug listed in the protocol**
- **Attach Investigator's Brochure**

72. Provide a detailed description of how FDA-regulated drugs/biologics will be stored, secured, dispensed, administered, tracked, and returned.

The Cleveland VA Research Pharmacy procures the study medication. It then stores, dispenses and tracks the study medication. If any study medication is returned to the PI, then he returns it to the Cleveland VA Research Pharmacy.

Section 10 – FDA-Regulated Devices

This section should be completed for a medical device that is the <u>subject</u> of a clinical study designed to evaluate the effectiveness and/or safety of the device.

- An investigational device may be an FDA approved device that is being studied for an unapproved use or efficacy. This also includes an approved device that is being studied for an unapproved or approved use in a controlled, randomized, or blinded clinical trial.
- Documentation of FDA approval for the experimental use of the device must be provided for review (industry sponsored protocol listing the IDE number, letter from the FDA, letter from industry sponsor, or other document and/or communication verifying the IDE for this study).

Device Risk Determination:

Significant Risk (SR) Device is an investigational device that: (1) is intended as an implant and presents a potential for serious risk to the health, safety, or welfare of a subject, or (2) is purported or represented to be for a use in supporting or sustaining human life and presents a potential for serious risk to the health, safety, or welfare of

a subject; or (3) is for a use of substantial importance in diagnosing, curing, mitigating, or treating disease, or otherwise preventing impairment of human health and presents a potential for serious risk to the health, safety, or welfare of a subject; or (4) otherwise presents a potential for serious risk to the health, safety, or welfare of a subject.

Non significant Risk (NSR) Device is a device other than a significant risk device.

The IRB is required to document the basis for risk determination based on the proposed use of a device in the research by considering the nature of the harm that may result from the use of the device. FDA has the ultimate decision in determining SR and NSR.

An M.D. must be part of the Research Team for all studies that involve the use of a device.

The Environment of Care Committee (EOC) must approve all research that involves electrically line-operated devices, which have leads or electrodes and will come in contact with human subjects.

73. Type of Product-check all that apply:

☒ **Not Applicable -No FDA-regulated devices involved – Proceed to Section 11)**

☐ **An FDA regulated device will be used BUT not with intent of studying safety or efficacy** (*Proceed to Section 11)*

☐ **Device**

74. List the device-include name and manufacturer:

75. FDA Regulatory Status of the Device:

☐ **FDA Approved Device**

- **A device approved by the FDA for distribution, marketing, sale to, and use by, the public for the study's indication.**

☐ **New Indication of an FDA Approved Device**

- **A device NOT approved by the FDA for distribution, marketing, sale to, and use by, the public for the indication used in the study.**

☐ **Investigational - Investigational Device Exemption (IDE)**

- **An FDA designation that permits a manufacturer to lawfully ship an unapproved device for use in a research study.**

Provide the following:

a. IDE Number:

b. IDE Sponsor or Holder:

If the PI holds the IDE, complete the following:

i. The PI reviewed the Guidance on Requirements of the Sponsor and the Investigator as Sponsor

☐ **Yes**

ii. As the PI, you will comply with the regulatory responsibilities of a sponsor

☐ **Yes**

c. FDA or Sponsor Device Risk Determination

☐ **Non-Significant Risk**

☐ **Significant Risk**

d. Attach documentation of FDA approval for the experimental use of the device (industry sponsored protocol listing the IDE number, letter from the FDA, letter from industry sponsor, or other document and/or communication verifying the IDE for this study).

☐ **Humanitarian Use Device (HUD)**

- **An FDA designation for a medical device intended to benefit patients in the treatment or diagnosis of a disease or condition that affects or is manifested in fewer than 4,000 individuals in the United States per year. For more information about Humanitarian Use Devices see the HRPP SOP manual on the R&D website.**

Provide the following:

a. HUD Number:

b. HUD Sponsor or Holder:

c. Include a copy of the FDA letter granting Humanitarian Use Device (HUD) status.

☐ **510(k) Status –**

- **A device determined by the FDA to be "substantially equivalent" to an existing device that is legally marketed in the U.S. Until a 510(k) device is approved, it is still considered investigational.**

a. Provide the name of an equivalent device and sufficient documentation to justify 510(k)

76. Attach device information (i.e., brochure, device label)

77. Provide a detailed description of how FDA-regulated devices will be stored, secured, dispensed, administered, tracked, and returned.

Section 11 – Genetic Testing and Discovery of Genetic Information (DNA)

78. Does the research involve genetic testing or DNA/RNA extraction?

☒ **No genetic testing** (*Proceed to Section 12)*

☐ **Yes- complete the following:**

a. Describe the purpose of the genetic testing component of the study

- *Is it to establish risks, associations, or prevalence?*

b. Describe whether the test is a standard test already in clinical use or a new or experimental laboratory study

c. Describe the accuracy of the test

- *Sensitivity, specificity, reliability, validity, and variability*

79. Does an abnormal test result indicate that the subject:

- ☐ **Has a specific condition**
- ☐ **Is at risk for a specific condition**
- ☐ **May be at risk for a specific condition**
- ☐ **Has, is, or may be at risk for some other outcome**
- ☐ **Other** *(describe):*

80. Does a normal test result indicate that the subject

- ☐ **Is not at risk for a specific condition**
- ☐ **Is at a lower risk for a specific condition**
- ☐ **Is at a population risk for a specific condition**

81. Is there a risk of discovery of other results such as non-parentage or other genetic conditions?

☐ **No** ☐ **Yes- please explain:**

82. Will test results produce information on anyone (e.g. a first-degree relative) besides the subject?

☐ **No** ☐ **Yes- please explain:**

83. To whom and in what manner will genetic information be reported?

84. Will genetic counseling be made available to subjects?

☐ **No** ☐ **Yes- indicate who will conduct the counseling and whether there are any additional charges:**

85. Will DNA samples be stored?

☐ **No** ☐ **Yes--describe where, how, and for how long the samples will be stored:**

86. Who will own the DNA samples?

87. Will there be any subsequent analysis of the DNA samples?

☐ **No** ☐ **Yes- describe the purpose of the subsequent analysis and whether there will be dissemination of any new information:**

88. Describe how samples will be handled if the subject withdraws consent for further participation:

89. Will the samples be distributed to other investigators?

☐ **No** ☐ **Yes- please explain:**

90. Describe the provisions to maintain the confidentiality of research data, especially in cases where data can be linked to individual subjects:

Section 12 – Tissue Collection/Storage/Banking*

It is VA policy to ensure that human biological specimens, as well as the linked data collected as part of research projects conducted by VA investigators in VA facilities or approved off-site locations, are maintained at *VA approved tissue banks or VA-sponsored tissue banks.

See VHA Directive 2000-043 "Banking of Human Research Subjects' Specimens" for more information and also visit http://www.research.va.gov/programs/tissue_banking/default.cfm

Human biological specimens (specimens).

- **Human biological specimens are materials, such as blood, urine, tissue, organs, hair, nail clippings, buccal swabs or any other materials that are derived from human subjects and are either collected specifically for research purposes or as residual specimens from diagnostic, therapeutic or surgical procedures.**

91. *Does the research involve storage or banking of human specimens or identifiable private information for use in future studies? *(check all that apply)*

☒ **No** *(proceed to Section 13)* ☐ **Yes-describe status of VA approved or VA sponsored facility:**

☐ **Storing or banking identifiable private information**

☐ **Storing or banking human specimens**

Please provide the following information:

a. **What identifying information will be required?**

b. **What are the foreseeable uses of the specimens (e.g., research, pharmaceutical products, production of cellular lines for various uses, etc.)?**

c. **What is the VA approved or VA sponsored location/institution where the information and/or specimens will be stored?**

d. **How long will the information and/or specimens be stored?**

e. **Is the storage facility an on-site or off-site location?**

f. **Will subjects be able to request that their specimen and/or information be withdrawn from the bank or repository?** *(explain)*

Section 13 – Children as Research Subjects

Research involving children must not be conducted by VA investigators while on official duty or at VA or VA-approved offsite facilities unless a waiver has been granted by the CRADO (See VHA Directive 2001-028 "Research Involving Children" for more information.

92. Do you plan to enroll children as research subjects?

☒ **No** *(Proceed to Section 14)*

☐ **Yes- Age range of subjects:**

93. Category of Research *(Check the box next to the category of research you believe your research falls under. The IRB will make a final category determination during review.)*:

☐ **Research involving minimal risk (the probability & magnitude of harm or discomfort anticipated are not greater than those ordinarily encountered in daily life or during routine physical or psychological tests.)** *(46.404)*

☐ **Research involving greater than minimal risk but of potentially direct benefit to the subject.** *(46.405)*

☐ **Research involving greater than minimal risk and no prospect of direct benefit to the subject but likely to yield generalizable knowledge about the subject's disorder or condition.** *(46.406)*

☐ **Research not otherwise approvable which presents an opportunity to understand, prevent or alleviate a serious problem affecting children/decisionally impaired adults.** *(46.407)*

94. Do you anticipate enrolling minors who are wards of the state?

☐ **No** ☐ **Yes**

95. Permission of parents or guardian *(check one only)*:

☐ **The permission of each child's parents or guardian will be sought unless one parent is deceased, unknown, incompetent, or not reasonably available, or when only one parent has legal responsibility for the care and custody of the child (required for categories 46.406 and 46.407 above in item 104).**

☐ **The permission of only one parent will be sought (acceptable for categories 46.404 or 46.405). If marked, provide justification:**

96. Assent of Children *(check one only)*:

☐ **The assent of each child who is capable of providing assent based on age, maturity, and psychological state will be sought.**

☐ **The assent of each child will not be sought because the capability of all of the children in this study population is so limited that they cannot reasonably be consulted. Explain why the capacity is so limited, e.g., age, maturity and/or psychological state:**

☐ **The assent of each child will not be sought because the intervention or procedure involved in the research holds out a prospect of direct benefit that is important to the health or well-being of the children and is available only in the context of the research. Explain what the direct benefit may be and why it is only available in the context of the research:**

Section 14 – Other

97. Please describe any other study procedures not referenced in the previous sections:

☒ **Not applicable**