NCT02737930
Fluoxetine for Visual Recovery after Ischemic Stroke

(FLUORESCE)

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1. PURPOSE AND BACKGROUND

1.1. Purpose

Primary Objective:

To test whether fluoxetine, a selective serotonin reuptake inhibitor (SSRI) previously demonstrated to enhance post-stroke motor recovery, also enhances post-stroke visual recovery in ischemic stroke survivors.

Secondary Objectives:

(1) To understand whether a putative fluoxetine effect is mediated through a drug-specific mechanism (*e.g.* a fluoxetine-dependent increase in neural plasticity), or rather through indirect mechanisms, such as general improvements in mood and motivation to participate in rehabilitation, resulting from the antidepressant actions of the drug.
(2) To track the natural history of post-stroke visual recovery using a combination of clinical and radiographic approaches, including standard neuro-ophthalmologic evaluations, measures of retinal nerve fiber layer (RNFL) thickness, visual and general disability measures, neuropsychological testing, and functional magnetic resonance imaging (fMRI).
(3) To estimate the feasibility of larger future clinical trials studying the effects of various pharmacological or behavioral interventions on the rate and degree of post-stroke visual recovery.
(4) To use the information gathered from the above objectives to study the physiologic mechanisms of spontaneous post-stroke visual recovery, with the goal of identifying better targets for therapeutic interventions.

1.2. Background

Current strategies in the treatment of ischemic stroke

Despite major advances in acute stroke care over the last two decades, ischemic stroke remains a leading cause of serious long-term disability (1), with 800,000 strokes expected in the United States this year alone. Some form of visual impairment, such as homonymous hemianopia, is present in one to two thirds of all stroke patients (2). Visual impairment, and in particular homonymous hemianopia, is associated with poor prognosis after stroke (3). Complete spontaneous recovery is uncommon (4) although there is some gradual return of visual function due to endogenous repair mechanisms in the first few months (5). At present, there are no proven treatments beyond the first several hours after a stroke that substantially improve functional outcomes. Two decades on, thrombolysis with intravenous (IV) recombinant tissue plasminogen activator (rt-PA) remains the gold standard of acute stroke care in the United States and elsewhere (6). Unfortunately, only 10% of ischemic stroke patients are eligible for this therapy, as the overwhelming majority

of stroke survivors do not present to a hospital within 3 to 4.5 hours of symptom onset. Furthermore, given that not all eligible patients are treated with IV rt-PA (*e.g.* 77% in 2011) (7), and only 12% of treated patients benefit (6), less than 1% of all ischemic stroke patients may ultimately owe their functional recovery to this time-sensitive treatment. Therapies that enhance recovery beyond the hyperacute stage of the injury have the potential to help a much larger proportion of stroke patients. However, no subacute therapy capable of enhancing post-stroke recovery across the spectrum of stroke etiology, severity, and symptomatology is currently available.

A possible role for SSRIs in improving functional outcomes in stroke survivors

Several lines of evidence suggest that SSRIs, and in particular fluoxetine, may improve functional outcomes in stroke survivors with moderate to severe motor deficits (8). We hypothesize that SSRIs mediate these effects by modulating neural plasticity and promoting cortical reorganization. One of the major shortcomings of previous studies investigating a role for SSRIs in post-stroke functional recovery has been their focus on clinical outcomes at the expense of physiologic outcomes. As a result, it has been difficult to attribute clinical benefits to mechanisms independent of the antidepressant and activating effects of these medications. In the Fluoxetine for Motor Recovery after Acute Ischemic Stroke (FLAME) trial (8), arguably one of the most compelling studies in this field of inquiry to date, the authors were careful to exclude patients with a history of depression and those on antidepressants at the time of their strokes. At 90 days, patients in the fluoxetine group had less depression, suggesting that these patients may have been more motivated to recover, but the apparent clinical benefit from fluoxetine in terms of motor recovery was still significant after the authors adjusted their analysis for the onset of depression during the study period. While suggestive of an independent role for fluoxetine in post-stroke recovery, these results do not constitute direct evidence of a separate, intervenable mechanism by which fluoxetine may enhance the recovery process in a manner independent of its antidepressant actions. Similarly another SSRI, escitalopram, has shown promise in improving post-stroke cognitive outcomes, specifically short-term memory, in ischemic stroke survivors (9), but the authors did not elucidate the physiologic mechanism of this apparent clinical benefit. We hope to resolve this issue by conducting a randomized clinical trial in which we will follow clinical and physiologic outcomes longitudinally in acute ischemic stroke patients with isolated visual field deficits treated with fluoxetine *vs.* placebo.

Using visual recovery to study the mechanisms of post-stroke functional recovery

The visual cortex offers the ideal model system for testing hypotheses about mechanisms of neural plasticity that may be engaged by SSRIs in the post-stroke recovery period. First, in contrast to motor recovery, motivation probably plays a less prominent role in post-stroke visual recovery, as most spontaneous recovery probably occurs early (10) and rehabilitative interventions typically focus on teaching patients compensatory techniques. Second, it is known that fluoxetine can reopen critical periods of neural plasticity in the adult rodent visual system (11). Third, structure-function relationships in the visual system are well understood. The early visual cortex in particular has a highly regular retinotopic organization. Post-stroke changes in this retinotopic map can be characterized and followed by fMRI. Furthermore, cerebral infarction can lead to retinal ganglion cell degeneration through a retrograde trans-neuronal mechanism (12), providing another window through which post-stroke changes in the visual pathway can be monitored and quantified using non-invasive techniques such as optical coherence tomography (OCT). Our research team has demonstrated expertise in characterizing early visual system organization in clinical populations (13). Thus, we are well positioned to assess whether

any observed effects of fluoxetine on post-stroke recovery are due to quantifiable changes in neuronal survival and neural plasticity.

Potential future directions

Fulfillment of this research program has the potential to alter our clinical approach to ischemic strokes affecting the visual system. In addition, answering these questions in the visual system may have more general implications. An understanding of the dynamics and limits of neural plasticity in the post-stroke visual cortex will likely enable us to formulate and test specific hypotheses about how therapeutic interventions like fluoxetine may promote recovery from ischemic strokes affecting other higher-order cognitive functions, including language, praxis, memory, attention, and executive function.

2. STUDY DESIGN

2.1. Overview

This will be a single-center randomized double-blind placebo-controlled clinical trial in which ischemic stroke patients with isolated hemianopia or quadrantanopia will be identified during their acute hospitalization and randomly assigned to a course of fluoxetine *vs.* placebo for 90 days. Baseline visual function will be assessed during the initial hospital admission using a battery of neurologic, ophthalmologic, behavioral, and radiographic measures. As post-stroke recovery tends to plateau by 6 months, patients will be followed for 6 months and evaluated using the same set of measures at 30 days, 90 days, and 6 months post-stroke in order to determine whether fluoxetine improves visual recovery.

2.2. Rationale for Study Design

Given the growing evidence that SSRIs may improve motor recovery in stroke survivors, we hypothesize that fluoxetine will also enhance post-stroke functional recovery in the visual system. We further hypothesize that this effect will be mediated through a mechanism independent of the antidepressant and activating effects of fluoxetine. In order to investigate these hypotheses, we have designed a clinical trial in which acute ischemic stroke patients with visual field deficits will be randomized in a 1:1 ratio to fluoxetine *vs.* placebo. The degree of improvement in visual function will then be directly compared between the treatment group and the control group. Because visual recovery after stroke usually plateaus in the first 6 months, we have chosen to treat study subjects for 90 days with fluoxetine *vs.* placebo to determine if exposure to SSRIs during the peak time of recovery improves the rate or degree of recovery. This is also the duration of treatment that was used in the FLAME trial (8).

2.3. Rationale for Dosage

Study subjects will be randomized to 20 mg of fluoxetine *vs.* placebo by mouth, taken on a daily basis for 90 days, starting within 72 hours of admission to the hospital. This dosage was chosen because it was shown to have an effect on post-stroke motor recovery in the FLAME trial (8). Furthermore, stroke patients tend to be older and therefore more likely to develop side effects at higher doses of the drug.

3. CHARACTERISTICS OF THE RESEARCH POPULATION

3.1. Subject Characteristics

a) **Number of Subjects:** The planned enrollment is 40 patients over 12 months in order to achieve a final sample size of 30 subjects, assuming a dropout rate of 25% during the course of the study. This projected sample size and time frame represent a conservative estimate based on the 56 acute ischemic stroke patients who were admitted to Strong Memorial Hospital with an isolated visual field deficit between January 1, 2015 and December 31, 2015. This sample size is comparable to equivalent pilot trials evaluating the efficacy of an approved drug for a novel indication. If any subjects withdraw from the study, they will be replaced to meet this enrollment goal.

b) **Gender and Age of Subjects:** Men and women between 18 and 85 years of age will be enrolled in the study. Patients older than 85 will be excluded because advanced age is associated with increased risk of adverse side effects from SSRIs. Furthermore, the ability to fixate and produce reliable visual field measurements deteriorates with increasing age.

c) **Racial and Ethnic Origin:** Subjects of all racial and ethnic backgrounds will be enrolled in the study.

d) **Vulnerable Subjects:** Subjects who are vulnerable to coercion or undue influence will not be enrolled, including children, pregnant women, students, employees, prisoners, and persons with decisional impairments.

3.2. **Inclusion and Exclusion Criteria**

a) **Inclusion Criteria:** Patients between 18 and 85 years of age who are admitted to Strong Memorial Hospital with an MRI-confirmed acute ischemic stroke resulting in a clinically verifiable isolated right-sided or left-sided homonymous hemianopia or quadrantanopia will be eligible for inclusion in the study.

b) **Exclusion Criteria:**
- Known hypersensitivity reaction to fluoxetine or other SSRIs
- National Institutes of Health Stroke Scale (NIHSS) score greater than 5
- Premorbid modified Rankin Scale (mRS) score greater than 2
- Premorbid monocular or binocular visual field deficits
- Premorbid retinopathy or optic neuropathy
- Premorbid depression
- History of cognitive impairment, dementia, or neurodegenerative disorder
- History of seizure disorder
- History of mania or hypomania
- History of hyponatremia
- History of angle-closure glaucoma or elevated intraocular pressure
- Current alcohol abuse or impaired liver function
- Current use of an antidepressant medication
- Current use of a medication likely to have an adverse interaction with fluoxetine
- Current use of a medication likely to impair post-stroke recovery
- Contraindication to MRI
- Pregnancy or lactation
- Hemorrhagic transformation of the index stroke, resulting in mass effect
- Enrollment in another clinical trial at the time of the index stroke

3.3. Discussion of Subject Population

In order to minimize risks to our study population, potential subjects will be excluded from participation in the study if they have a known contraindication to a component of the study protocol, such as a drug allergy to fluoxetine or other SSRIs, concomitant use of a medication that may interact with SSRIs, or contraindication to MRI. Because of potential risks to the fetus and nursing infants, pregnant and lactating women will also be excluded. Pre-menopausal women will only be included if the initial urine pregnancy test is negative and they commit to using birth control for the duration of the drug administration phase of the study (first 90 days). Patients with impaired liver function or advanced age (greater than 85 years old) will be excluded due to the possibility of impaired fluoxetine metabolism.

Additionally, we will exclude any subject with a condition that may interfere with the interpretation of the study results, such as premorbid depression, previously identified visual field deficit of any cause, concurrent use of medications known to impair post-stroke recovery, high initial NIHSS score, or hemorrhagic transformation of the index stroke resulting in a hematoma large enough to cause mass effect (corresponding to an ECASS score of PH1 or PH2) (14), as these conditions are associated with poor functional outcome.

Finally, because automated Humphrey perimetry requires the subject to be able to follow multi-step commands and maintain visual fixation for 20 minutes, potential subjects with impaired cognition or attention, or premorbid mRS score greater than 2, will be excluded.

4. SUBJECT IDENTIFICATION, RECRUITMENT, AND CONSENT

4.1. Method of Subject Identification and Recruitment

Potential subjects will be identified by Neurology and Ophthalmology residents, fellows, and attending physicians at Strong Memorial Hospital. When a candidate is identified, a member of the medical team will ask the patient if he or she would be interested in being approached by study personnel during the hospital admission in order to find out more about the study. If the patient expresses interest, the study coordinator and one of the investigators will meet with the patient and family to describe the study and obtain consent. In order to minimize undue influence, members of the medical team (*i.e.* the attending physician of record and the on-service stroke fellow) will not be involved in the consent process. Instead, an investigator not directly involved in the patient's care will be responsible for discussing the study with the potential subject and obtaining consent.

4.2. Process of Consent

An investigator will obtain written informed consent from each subject before the performance of any procedure related specifically to the study protocol. The protocol will be reviewed with each candidate, highlighting the differences between study-specific procedures and routine studies performed as part of standard care, so that he or she can make an informed decision about participation in the study. When possible, potential study participants will be approached early during their hospital course to ensure sufficient time to address any questions or concerns. We do not anticipate enrolling any non-English speaking subjects.

Each signed consent form will be kept in the study binder in a locked drawer in the Principal Investigator's office (Room 5.5722A). This is a locked room in an office suite that requires badge access for entry. A separate fMRI consent form will be used for any fMRI studies performed at the Rochester Center for Brain Imaging (RCBI). This consent will be administered by RCBI staff on the day of the procedure and stored securely in accordance with RCBI protocols.

5. METHODS AND STUDY PROCEDURES

Subjects will be evaluated at five time points as indicated in the Table: at baseline (*i.e.* during the acute hospitalization immediately after enrollment in the study) and at 7 days, 30 days, 90 days, and 6 months after randomization. They will be contacted by phone 7 days after the initiation of the study drug to screen for any adverse events using an adverse event questionnaire (Appendix H). This questionnaire will be administered in the hospital if the patient has not been discharged yet, and repeated at the remaining time points.

At baseline, the premorbid mRS, Patient Health Questionnaire-9 (PHQ-9), and Visual Function Questionnaire-25 (VFQ-25) scores will be determined for each subject. As part of standard care, subjects will undergo a formal neuro-ophthalmological examination to confirm and characterize their visual field deficits. This will also help to rule out ocular, motor, or cognitive deficits likely to impair their ability to perform the visual function tests required by the study protocol. In addition, subjects will be evaluated by ocular coherence tomography to determine baseline RNFL thickness, neuropsychological testing to assess their ability to perform certain visual tasks, and fMRI for retinotopic mapping of the early visual cortex. To ensure that potential subjects do not have any hematologic abnormalities (*e.g.* thrombocytopenia) or metabolic derangements (*e.g.* hyponatremia, hepatic insufficiency) that may affect the safety of taking fluoxetine, all candidates will have a complete blood count (CBC) and comprehensive metabolic panel (CMP) drawn at baseline. Women of childbearing age will have a urine pregnancy test to make sure they are not pregnant. Finally, because some SSRIs like citalopram have been associated with QT interval prolongation, each patient's baseline electrocardiogram (ECG) will be assessed for possible arrhythmias prior to randomization.

Subjects will be started on fluoxetine *vs.* placebo within 5 days of the index stroke and no later than 72 hours after their admission to the hospital. Seven days after randomization, they will be called by telephone and assessed for any adverse events using a questionnaire. If the subject has not been discharged from the hospital yet, this assessment will be performed in person in the hospital. Subjects will return for study-specific and routine evaluations at 30 days, 90 days, and 6 months following the initiation of treatment. During these visits, they will undergo assessments that constitute standard care as well as study-specific evaluations and monitoring, as indicated in the Table.

5.1. Treatment Dosage and Administration

Subjects will be randomized in a 1:1 ratio to 20 mg of fluoxetine *vs.* placebo. Fluoxetine is an oral medication and is usually taken in the morning because of its possible stimulant effects. The University of Rochester Medical Center Investigational Drug Service will prepare and provide fluoxetine or placebo to all subjects. They will administer the study drug to each study participant during the hospital admission. At discharge, each study

participant will be given enough study drug to last until the end of the study. The study drug will be discontinued without a taper at the end of 90 days. Drug accountability logs will be updated during routine follow-up visits at 30 and 90 days.

5.2. **Efficacy Assessments**

To assess the effect of fluoxetine on post-stroke visual recovery, subjects will be evaluated by a formal neuro-ophthalmologic examination, automated Humphrey perimetry, OCT, neuropsychological testing, fMRI, and various clinical scales and questionnaires (mRS, PHQ-9, and VFQ-25) following the schedule outlined in the Table. Functional vision will be assessed by calculating the functional vision score as described in the Guide for the Evaluation of Visual Impairment, prepared on behalf of the International Society for Low Vision Research and Rehabilitation (15).

1. Modified Rankin Scale (mRS): The most commonly used outcome measure in stroke clinical trials, the mRS is a tool designed to quantify disability in stroke patients based on their level of independence in the activities of daily living (Appendix E). It requires 5 minutes to perform and will be administered by certified faculty, fellows, and residents from the Department of Neurology. Scores range from 0 (no symptoms) to 6 (death). Documentation of the mRS score at baseline and outpatient follow-up is part of standard care.

2. Neuro-ophthalmologic examination: This is a standardized clinical evaluation to be performed by study investigator, Dr. Zoe Williams, at the University of Rochester Flaum Eye Institute. It consists of an external eye exam, pupillary exam, dilated fundoscopic exam, standard neurologic exam, and an evaluation of visual acuity, refraction, color vision, sense of brightness, visual field size, and ocular motility. A baseline neuro-ophthalmologic evaluation represents standard care in the assessment of patients with new visual field deficits attributable to an acute ischemic stroke.

3. Automated Humphrey perimetry: Humphrey perimetry is an automated non-invasive clinical test performed in most routine ophthalmologic evaluations to characterize and monitor a patient's peripheral vision, using normative data from healthy age-matched controls as a reference. In this study, we will use Swedish Interactive Threshold Algorithm (SITA) standard 24-2 visual field testing to assess each subject's peripheral vision at the specified time points. This form of automated Humphrey perimetry requires 7 ½ minutes of testing time. Testing will be performed by a qualified ophthalmic technician or physician at the University of Rochester Flaum Eye Institute. During each test, the subject will place his or her chin on a chin rest, fixate on a central point, and respond with a push-button when he or she sees a test spot presented briefly in the peripheral visual field. Baseline, 90-day, and 6-month assessments represent standard care, whereas the 30-day assessment is for research purposes only.

4. Optical coherence tomography (OCT): This is a standardized non-invasive clinical test that uses light waves to measure the thickness of the RNFL in patients with a wide range of visual problems. It requires 30 seconds of testing time. It will be performed by a qualified ophthalmic technician or physician at the University of Rochester Flaum Eye Institute. OCT is not part of standard care for this patient population.

5. Patient Health Questionnaire-9 (PHQ-9): This is a self-report inventory used as a screening and diagnostic tool for depression (Appendix F). The 9 items are based on

the 9 diagnostic criteria for depression included in the Diagnostic and Statistical Manual of Mental Disorders IV. It takes 5-10 minutes to complete. It will be administered at baseline, 30 days, 90 days, and 6 months. The 30- and 90-day assessments will be performed during routine follow-up in the University of Rochester Stroke and Cerebrovascular Disorders Clinic. The 6-month assessment will be performed by phone interview. Screening for depression by PHQ-2, a shorter version of PHQ-9, is part of standard care for this patient population at baseline. However, screening by PHQ-9 is not part of standard care at baseline or at any other study time point.

6. Functional vision assessment: This will be done by calculating the functional vision score for each subject as described in the Guide for the Evaluation of Visual Impairment (15), a clinical and research tool designed to measure functional vision in adults with acquired vision loss. Calculation of a functional vision score using this tool requires visual field and visual acuity assessments, so it will be done at baseline and at 6 months by study investigator, Dr. Zoe Williams, at the University of Rochester Flaum Eye Institute. Ophthalmologic follow-up at these time points is part of standard care.

7. Visual Function Questionnaire-25 (VFQ-25): This is a 25-item survey designed to provide a vision-targeted assessment of health-related quality of life by measuring the influence of visual disability on daily visual functioning, emotional well-being, and social functioning (Appendix G). It takes 10 minutes to complete. It will be administered at baseline and 6 months. The 6-month assessment will be performed by phone interview. Assessing vision-related quality of life by VFQ-25 is not part of standard care for this patient population.

8. Neuropsychological testing: The neuropsychological assessment will consist of picture naming tasks, face memory tasks, and other simple tests of low- and high-level visual processing, such as indicating whether a stimulus is seen on a screen. The participant's eye position will be monitored using special cameras during certain tests. Some tests will require participants to indicate the location of a stimulus on a screen with their fingers. For these tests, finger position during the pointing motion will be tracked using a special camera system. Neuropsychological testing will be performed at baseline, 30 days, 90 days, and 6 months by study investigator, Dr. Bradford Mahon, and members of his laboratory. The baseline assessment will be completed before discharge from the hospital and require approximately 45 minutes. Subsequent sessions will occur at the RCBI and will require approximately 90 minutes each. Neuropsychological testing is not part of standard care for this patient population.

9. Functional magnetic resonance imaging (fMRI): Visual processing will be assessed using fMRI. Dependent measures will consist of high-resolution measurements of cortical thickness and representation, functional activity during visual tasks as measured by blood oxygen level-dependent (BOLD) responses, and measurements of the structural integrity of nerve fibers in the brain using diffusion tensor imaging. Subjects will be asked to view and respond to a visual stimulus according to the specific task description. For example, they may be asked to name common objects depicted in a picture, or estimate the number of dots in a display. Typically subjects will be asked to perform a task in the MRI machine for 45 minutes, although sessions may go up to 70 minutes depending on the comfort and compliance of the study participant. Tasks will be broken up into shorter runs of 5 to 10 minutes in order to

allow participants to rest during the testing session. Scanning will occur on MRI machines at Strong Memorial Hospital, the University of Rochester Stroke and Cerebrovascular Disorders Clinic, or the RCBI. Study integrity will not be compromised by scanning a given patient on different scanners at different times. We will compute contrasts only between experimental conditions tested on the same machine during the same scan, so the key effects we measure will be orthogonal to any scanner variation. Finally, fMRI data will be retained in an anonymized form for future use by other researchers as part of this study.

5.3. Safety Assessments

Subjects will be instructed to exercise caution when drinking alcohol or taking any previously prescribed sedating medications, such as diphenhydramine or cyclobenzaprine, while on the study drug. Additionally, they will be advised to contact their primary care physicians or the study team before starting any new prescription or over-the-counter medications, or any new herbal or nutritional supplements. Primary care physicians will be provided with a list of medications and supplements to avoid while their patients are on the study drug.

Laboratory studies: A CBC and CMP will be repeated 30 days after the initiation of the study drug to monitor for any hematologic or metabolic abnormalities. This will require a total of 9 mL of blood to be collected from each subject.

ECG: An ECG will be obtained at baseline and at 30 days to measure each subject's QT interval and monitor for QTc prolongation or other arrhythmias.

Adverse event survey: A questionnaire to screen for adverse events will be administered by study personnel at 7 days by phone interview (Appendix H). This 7-day evaluation will be done in person if the patient has not been discharged from the hospital yet. The same questionnaire will be administered when the subjects return to the University of Rochester Stroke and Cerebrovascular Disorders Clinic for their follow-up visits at 30 and 90 days. Finally, the same questionnaire will be administered at 6 months by phone interview.

5.4. Data and Specimen Banking for Future Research Use

The data generated in this study may be used in future research in an anonymized form that cannot be connected to any individual subject. Data may also be shared with other researchers, but only after all identifying information has been removed to ensure subject confidentiality. Information recorded on paper will be stored inside a locked cabinet in a locked office as previously described. All digital data will be password-protected and stored on a firewalled server.

5.5. Costs to the Subject

There will be no planned costs to the subject for participation in this study. All study drugs will be provided free of charge. Neurological and neuro-ophthalmological evaluations performed as part of standard care at baseline, 30 days, 90 days, and 6 months will be billed to the patient's insurance. Additional study-specific evaluations that fall outside standard care (see Table) will be covered by the research program. Should a subject suffer any adverse outcomes as a result of participation in the study, the subject and/or the subject's insurance may need to cover the costs of any additional medical treatment

required.

5.6. Payment for Participation

Upon completing the study, each subject will receive a $50 Visa® prepaid debit card as a token of appreciation for his or her participation. In addition, parking expenses will be covered for all follow-up visits.

5.7. Return of Individual Research Results

Individual research results will not be routinely made available to study subjects. However, they will have access to many of their test results upon request or through the online patient medical record access system, MyChart. With the exception of the serial fMRI studies, baseline and 60-day OCT studies, the PHQ-9, VFQ-25, and adverse event questionnaires, and the ECG, CBC, CMP, and Humphrey visual field testing performed at 30 days, all proposed evaluations are part of the routine care and work-up of stroke patients with visual field deficits. Results of these evaluations will be included in the medical record. Any incidental findings of potential clinical significance, discovered in the course of a study-specific evaluation that falls outside standard care, will be immediately disclosed to the patient and his or her primary care physician. Follow-up studies or consultations will also be recommended to the primary care physician as appropriate.

6. CONCOMITANT AND DISALLOWED MEDICATIONS

Subjects will be randomized to 20 mg of fluoxetine *vs.* placebo as previously described. During the course of the study, they will not be allowed to take higher doses of fluoxetine or any other SSRIs. Additionally, in order to reduce the risk of any adverse events due to drug-drug interactions, they will not be allowed to take medications contraindicated in combination with SSRIs, including other SSRIs, non-selective serotonin reuptake inhibitors, monoamine oxidase inhibitors, tricyclic antidepressants, and QTc-prolonging agents.

7. SUBJECT WITHDRAWALS

Subjects will be advised on the written informed consent form (Appendix A) that they have the right to withdraw from the study at any time without prejudice. Subjects may also be withdrawn from the study by study investigators if they have a recurrent stroke, a symptomatic hemorrhagic transformation of the index ischemic stroke, or another major illness requiring hospitalization, if they become pregnant, or if they are not able to comply with the study protocol or return for routine and study-specific neurological or ophthalmological assessments. Subjects withdrawn from the study will be replaced.

8. STUDY DRUG ADMINISTRATION AND ASSIGNMENT

8.1. Study Drug

Fluoxetine is an antidepressant medication approved by the U.S. Food and Drug Administration (FDA) for use in several conditions, including major depressive disorder and obsessive-compulsive disorder. During the study, each subject will take 20 mg of

fluoxetine or a matching placebo daily for 90 days. Blinded capsules, identical in appearance and containing either an active dose or a placebo, will be prepared by over-encapsulation. Active doses will consist of a single 20-mg fluoxetine capsule placed inside a larger opaque colored capsule and backfilled with inert lactose powder. Placebo doses will consist of the same opaque colored capsule filled only with lactose. Exemption from Investigational New Drug (IND) regulations was granted by the FDA for the use of fluoxetine in this study on August 18, 2015.

8.2. Dosage of Study Drug

Fluoxetine will be administered by mouth at a daily dose of 20 mg for 90 days. There are no plans to increase or decrease the dose of the drug during the course of the study.

8.3. Subject Enrollment and Randomization

Subjects will be randomized in a ratio of 1:1 to fluoxetine *vs.* placebo by computer randomization. All study personnel will remain blinded to treatment assignments until the conclusion of the entire study, with the exception of the pharmacist and the statistician. These individuals will not disclose any information regarding the treatment assignment of individual subjects to the study investigators.

8.4. Accountability of Investigational Drug Supplies

The active drug and placebo will be prepared by the University of Rochester Medical Center Investigational Drug Service, which will also administer the drug to study participants during their hospital admission. Remaining doses of the drug will be given to each subject at the time of hospital discharge. From that point forward, the subject will be responsible for storing and administering the drug as an outpatient.

8.5. Discontinuation of Study Drug by Subject

Subjects will be free to stop the study drug at any time. Should they do so, they will be withdrawn from the study.

8.6. Emergency Drug Disclosure

The University of Rochester Medical Center Investigational Drug Service will maintain a list of treatment assignments for each subject and disclose this information upon request in case of a medical emergency. Should drug disclosure occur, the subject in question will be withdrawn from the study.

9. SAFETY AND REPORTABLE EVENTS

9.1. Adverse Event Definition

An adverse event is any symptom, sign, illness, or medical experience that develops or worsens during the course of the study, whether it is attributable to the study drug or not.

9.2. Serious Adverse Event

A serious adverse event is defined as an adverse medical experience that is life-threatening, results in death, requires hospitalization or prolongs an ongoing hospitalization, results in persistent or significant disability or incapacity, and/or requires a medical or surgical intervention to prevent permanent injury or impairment.

9.3. Recording Adverse Events

As specified in the Table, study personnel will screen each subject for adverse events at 7 days, 30 days, 90 days, and 6 months by recording all voluntary complaints of the subject, administering the adverse event questionnaire, and evaluating any available objective clinical findings.

All adverse events, whether observed by study personnel, or elicited from or volunteered by the subject, will be documented. Documentation will include a brief description of the experience, the date of onset, the date of resolution, the duration and type of experience, the severity, any relationship to the study drug, any contributing or alleviating factors, and any action taken with respect to the study drug.

9.4. Responsibilities for Reporting Serious Adverse Events

The Principal Investigator will record all serious adverse events that occur during the study period in an adverse event log. The study period for reporting serious adverse events will be from the time of signing consent until the final study visit at 6 months (*i.e.* 3 months after stopping the study drug). The Principal Investigator will comply with all RSRB policies and regulations regarding the reporting of adverse events.

10. RISK/BENEFIT ASSESSMENT

10.1. Potential Risks and Protection against Risks

Fluoxetine: Potential risks associated with the use of fluoxetine include allergic reaction, anaphylactic shock, depression, suicidal behavior, mania, seizures, serotonin syndrome, neuroleptic malignant syndrome, QT interval prolongation, acute angle-closure glaucoma, abnormal bleeding due to impaired platelet function, hypotension, hyponatremia, and priapism. More commonly, patients report insomnia, headache, anxiety, irritability, dry mouth, tremor, decreased libido, delayed ejaculation, and gastrointestinal symptoms such as nausea, indigestion, constipation, or diarrhea. These side effects typically resolve upon discontinuation of the drug. Subjects will be screened for depression during their enrollment in the study. If, at any point, they are diagnosed with depression, they will be referred to a health care provider for counseling and treatment. If they report suicidal thoughts, they may be directed to the Emergency Department for further evaluation.

Automated Humphrey perimetry, OCT, and neuropsychological testing: The risk associated with these procedures is minimal, the main risk being slight stress, fatigue, or boredom. To minimize these risks, subjects will be encouraged to take breaks, stop the evaluation, or leave the study at any time as they feel necessary. They will also be allowed to bring a family member or companion to the visit. These options will be explained clearly to all subjects prior to enrollment and during the course of the study.

MRI: There are no immediate risks associated with exposure to magnetic fields of 3.0 Tesla. Since the MR gantry is a small opening approximately 3 feet in diameter, the subject may experience anxiety, claustrophobia, or dizziness once he or she is placed inside the MRI machine. In addition, the functional scanning coil closely encloses the subject's head, potentially increasing the likelihood of claustrophobia. To mitigate these risks, the MR gantry is equipped with a camera allowing continuous monitoring of the subject from the control room at all times. In addition, the subject is given a pneumatic bulb that initiates an alarm in the control room when squeezed by the subject in case of an emergency. Furthermore, the subject is able to communicate through an intercom with the operator. Should the subject feel any discomfort, the experiment will be terminated promptly upon his or her request.

Subjects will be screened for magnetic material before each study using an MRI safety screening form (Appendices D1, D2, and D3). Those with pacemakers, implantable cardiac defibrillators, aneurysm clips, penile implants, metallic prostheses including heart valves and cochlear implants, and bullet or shrapnel fragments are at risk of injury in an MR environment. Welders and metal workers are also at risk because of possible metal fragments in their eyes. Those at risk will be excluded from the study.

Scanning by MRI produces a loud tone that can cause injury to the inner ear if appropriate protection is not used. Earplugs or close-fitting silicone-padded headphones will be provided to each subject to prevent ear injury.

The long-term health risks of MRI are unknown. This study will use a magnetic field strength of 3.0 Tesla, which is commonly used in clinical practice and research. This field strength has been used in the clinical setting for nearly a decade, and so far no detrimental long-term effects have been identified.

Phlebotomy: Risks associated with phlebotomy include pain or stinging when the needle is inserted and throbbing and/or bruising at the puncture site after the blood is drawn. To reduce the risk of bruising, subjects will be instructed to hold pressure on the puncture site for several minutes after the needle is withdrawn. Rarely the vein may become inflamed after the blood sample is obtained. This is treated with a warm compress applied several times a day. Finally, there is a small risk of infection at the puncture site. This risk will be minimized by the use of proper sterile technique.

10.2. Potential Benefits to Subjects

Patients randomized to the fluoxetine arm of the study may have improved visual recovery. They also may benefit from the antidepressant effects of fluoxetine. All subjects, whether they are in the fluoxetine or placebo arm, may benefit from depression screening, as depression is common after stroke and associated with poor recovery.

10.3. Alternatives to Participation

Patients may choose not to participate in the study. Unfortunately there are no proven therapies known to enhance post-stroke visual recovery at this time. Standard care for stroke patients with visual field deficits includes occupational and cognitive rehabilitation, which will be offered to all patients regardless of their participation in the study.

11. CONFIDENTIALITY OF DATA AND INFORMATION STORAGE

Subjects' names or initials will not be used when working with the data. Each subject will be assigned a label to maintain confidentiality. While we will make every effort to maintain confidentiality, it cannot be absolutely guaranteed as consent forms and other records that identify study subjects may be inspected by the Department of Health and Human Services and/or authorized officials of the University of Rochester. However, in no case will personal information be shared with other individuals or groups without written prior authorization from the subject. The results of this study may be presented at scientific meetings, published, shared with other researchers, or used in future studies, but data will be maintained in an anonymized form that cannot be connected to any individual subject. Information recorded on paper will be stored inside a locked cabinet in a locked office. All digital data will be password-protected and stored on a firewalled server.

12. RESEARCH INFORMATION IN MEDICAL RECORDS

Most of the data collected during this study will be part of the subject's medical record, including the initial diagnostic MRI, all automated Humphrey perimetry and OCT studies, all ECG studies, and all clinical exam and laboratory findings. The subject's participation in the study will also be documented in the medical record. The results of the neuropsychological assessment, fMRI testing, adverse event questionnaire, PHQ-9 and VFQ-25 questionnaires, and functional vision assessment will not be included in the medical record, but stored in the subject's study binder.

13. DATA ANALYSIS AND MONITORING

13.1. Sample Size Determination

The currently planned enrollment target of 40 subjects (*i.e.* 20 subjects per arm) is intended to achieve a final sample size of 30 and assumes a dropout rate of 25% during the course of the study. In turn, this estimate is based on the number of acute ischemic stroke patients who presented to Strong Memorial Hospital with an isolated visual field deficit in the previous calendar year (56 patients between January 1, 2015 and December 31, 2015). Previous studies indicate that 50% of patients will experience an improvement in their visual field deficit by 3 months. Based on this rate of spontaneous recovery, a final sample size of 15 subjects per group will provide 80% power to detect an improvement rate of 90% in the actively treated group (*i.e.* a 40% difference between the fluoxetine and placebo groups), using a one-sided χ^2 test with $\alpha = 0.05$. Thus, the planned sample size will be sufficient to detect a moderately large effect and is comparable to sample sizes used in equivalent pilot trials evaluating the efficacy of an FDA-approved drug for a novel application.

13.2. Planned Statistical Analysis

The primary endpoint will be an improvement in peripheral vision of at least 15 degrees in the affected visual field as measured by automated Humphrey perimetry at 6 months. The primary outcome will be compared between the treatment groups using an upper-tailed two-sample t test with $\alpha = 0.05$. Secondary outcome measures will include degree of cortical reorganization as assessed by fMRI, RNFL thickness as assessed by OCT, the functional vision score as assessed by the Guide for the Evaluation of Visual Impairment,

performance on neuropsychological testing, and scores on the mRS, PHQ-9, and VFQ-25.

13.3. Data and Safety Monitoring

A data and safety monitoring plan appropriate to the nature, size, and complexity of the study will be used to ensure: 1) an adequate process is in place for the oversight and monitoring of the conduct and progress of the study; 2) important information that may affect the safety or welfare of study subjects is noted and addressed as quickly as possible; and 3) the validity and integrity of the data are protected. The monitoring of data quality and subject safety will follow the National Institute of Neurologic Disorders and Stroke Guidelines for Data and Safety Monitoring in Clinical Trials.

The Principal Investigator will monitor the following elements of the study as part of this data and safety monitoring plan:

- Flow of data acquisition
- Timeliness and completeness of reporting
- Recruitment rates
- Protocol violations
- Serious adverse events

The number and nature of adverse events will be reviewed on a monthly basis by the Principal Investigator, and data will be un-blinded if there is serious concern about either of the treatment groups.

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TABLE. Schedule of tests and procedures

Procedure	Baseline	7 days	30 days	90 days	6 months
History & Physical	■				
Brain MRI[a]	■				
Urine pregnancy test[b]	●				
Complete blood count	■		●		
Comprehensive metabolic panel	●		●		
Electrocardiogram	■		●		
Modified Rankin Scale	■		■	■	
Neuro-ophthalmological exam	■				
Automated Humphrey perimetry	■		●	■	■
Optical coherence tomography	●				●
Functional vision score	●				●
Visual Function Questionnaire-25	●				●
Neuropsychological testing	●		●	●	●
Functional MRI	●		●	●	●
Patient Health Questionnaire-9	●		●	●	●
Adverse event questionnaire		●	●	●	●

[a] Magnetic resonance imaging
[b] For women of childbearing age only

■ Standard care
● Study-related procedure

APPENDICES.

A. Consent form (included separately)

B. Fluoxetine package insert (included separately)

C. Letter to primary care physicians

D. MRI safety screening forms

D1. Strong Memorial Hospital

D2. University Medical Imaging

D3. Rochester Center for Brain Imaging

E. Modified Rankin Scale

F. Patient Health Questionnaire-9

G. Visual Function Questionnaire-25

H. Adverse event questionnaire

I. Authorization to release medical information

J. List of study personnel

APPENDIX A. Consent form

APPENDIX B. Fluoxetine package insert

APPENDIX C. Letter to primary care physicians

601 Elmwood Avenue, Box 681
Rochester, New York, 14642
Phone: (585) 275-2530
Fax: (585) 273-1026

Primary care physician's name
Address line 1
Address line 2
Address line 3

Date

Dear Dr. _____,

Mr./Ms. _____ was admitted to Strong Memorial Hospital recently for an acute ischemic stroke resulting in a visual field deficit. He/She has consented to participate in a randomized double-blind placebo-controlled clinical trial testing the effect of fluoxetine (20 mg administered daily for 90 days) on post-stroke visual recovery. The study protocol involves serial visual field testing, optical coherence tomography, and functional magnetic resonance imaging studies to track the recovery process over the first 6 months after stroke.

In order to minimize the risk of any serious drug-drug interactions, Mr./Ms. _____ was advised to contact you or the study team before starting any new prescription or over-the-counter medications, or any new herbal or nutritional supplements. For your convenience, we have attached a list of medications and supplements that should be avoided while your patient is on the study drug during the first 90 days of the study. In addition to these medications, the use of any pharmaceutical agents likely to impair post-stroke recovery, including benzodiazepines and barbiturates, should also be avoided in the first 6 months.

Thank you in advance for your time and assistance. Please do not hesitate to contact me with any questions or concerns.

Sincerely,

[Signature]

Bogachan Sahin, MD, PhD
Principal Investigator, FLUORESCE Study
Assistant Professor, Department of Neurology
University of Rochester School of Medicine and Dentistry

List of medications to be avoided during the study

To minimize the risk of serious drug-drug interactions and possible impairment of post-stroke recovery, the following medications, herbs, and supplements should be avoided while your patient is in this study. If, in your opinion, the patient develops an indication for one of these medications during the first 90 days of the study, he or she may need to stop taking the study drug and withdraw from the study.

Selective and non-selective serotonin reuptake inhibitors, including citalopram, duloxetine, escitalopram, fluoxetine, fluvoxamine, paroxetine, sertraline, trazodone, venlafaxine, vilazodone.

Monoamine oxidase inhibitors, including isocarboxazid, linezolid, methylene blue, moclobemide phenelzine, procarbazine, rasagiline, selegiline, tranylcypromine.

Tricyclic antidepressants, including amitriptyline, nortriptyline, desipramine, imipramine.

Medications that prolong the QT interval, including amiodarone, azithromycin, ciprofloxacin, dofetilide, dronedarone, erythromycin, haloperidol, levofloxacin, moxifloxacin, pimozide, quetiapine, sotalol, thioridazine, ziprasidone.

Medications that may enhance the levels or toxic effects of fluoxetine, including abiraterone acetate, alfalfa, anise, aripiprazole, bilberry, buspirone, cimetidine, clarithromycin, dapoxetine, dextromethorphan, ethanol, fosphenytoin, ivabradine, linezolid, lithium, methylene blue, metoclopramide, mifepristone, ondansetron, propafenone, St. John's wart, tramadol, tryptophan, ziprasidone.

Medications that may diminish the levels or therapeutic effects of fluoxetine, including carbamezapine, dabrafenib, non-selective non-steroidal anti-inflammatory drugs.

Medications whose levels or toxic effects may be enhanced by fluoxetine, including aripiprazole, atomoxetine, carbamezapine, chlorpromazine, cilastazol, clozapine, dosulepin, conventional doxorubicin, flecainide, fosphenytoin, haloperidol, mequitazine, methadone, metoprolol, mexiletine, non-selective non-steroidal anti-inflammatory drugs, propafenone, tizanidine, tramadol, vinblastine, vortioxidine.

Medications whose levels or therapeutic effects may be diminished by fluoxetine, including clopidogrel, codeine, iobenguane I 123, tamoxifen.

Medications that may impair post-stroke recovery, including phenytoin, benzodiazepines, and barbiturates.

APPENDIX D1. MRI safety screening form (Strong Memorial Hospital)

APPENDIX D2. MRI safety screening form (University Medical Imaging)

APPENDIX D3. MRI safety screening form (Rochester Center for Brain Imaging)

APPENDIX E. Modified Rankin Scale

0	No symptoms
1	No significant disability, able to perform previous activities despite some symptoms
2	Slight disability, able to look after own affairs, but unable to perform previous activities
3	Moderate disability, requiring some amount of help, but able to walk without assistance
4	Moderately severe disability, unable to walk or attend to bodily needs without assistance
5	Severe disability, requiring constant care, bedridden, incontinent
6	Death

APPENDIX F. Patient Health Questionnaire-9 (PHQ-9)

PATIENT HEALTH QUESTIONNAIRE-9 (PHQ-9)

Over the last 2 weeks, how often have you been bothered by any of the following problems? *(Use "✔" to indicate your answer)*	**Not at all**	**Several days**	**More than half the days**	**Nearly every day**
1. Little interest or pleasure in doing things	0	1	2	3
2. Feeling down, depressed, or hopeless	0	1	2	3
3. Trouble falling or staying asleep, or sleeping too much	0	1	2	3
4. Feeling tired or having little energy	0	1	2	3
5. Poor appetite or overeating	0	1	2	3
6. Feeling bad about yourself — or that you are a failure or have let yourself or your family down	0	1	2	3
7. Trouble concentrating on things, such as reading the newspaper or watching television	0	1	2	3
8. Moving or speaking so slowly that other people could have noticed? Or the opposite — being so fidgety or restless that you have been moving around a lot more than usual	0	1	2	3
9. Thoughts that you would be better off dead or of hurting yourself in some way	0	1	2	3

FOR OFFICE CODING 0 + _____ + _____ + _____

=Total Score: _____

If you checked off any problems, how difficult have these problems made it for you to do your work, take care of things at home, or get along with other people?

Not difficult at all	**Somewhat difficult**	**Very difficult**	**Extremely difficult**
☐	☐	☐	☐

APPENDIX G. Visual Function Questionnaire (VFQ-25)

APPENDIX H. Adverse event questionnaire

Please indicate if you have had any of the following symptoms since starting the study drug by placing a check mark ☑ in the appropriate box.

☐Weight gain
☐Weight loss
☐Poor appetite
☐Increased appetite
☐Fatigue
☐Night sweats
☐Cold sweats during the day
☐Excessive daytime sweating
☐Hot or cold spells
☐Abnormal sensitivity to heat
☐Abnormal sensitivity to cold
☐Excessive sleeping
☐Excessive daytime sleepiness
☐Excessive thirst
☐Excessive urination
☐Flu-like symptoms
☐Vague sick feeling
☐Restlessness
☐Depressed mood
☐Suicidal thoughts
☐Forgotten periods of time
☐Loss of consciousness
☐Imbalance
☐Incoordination
☐Light-headedness
☐Spinning sensation
☐Memory impairment
☐Seizures or convulsions
☐Tics
☐Tremors
☐Muscle spasms
☐Numbness
☐Tingling
☐Slurred speech
☐Word-finding difficulty
☐Impaired attention
☐Impaired concentration
☐Confusion
☐Limb weakness
☐Falls

☐Cough
☐Wheezing
☐Shortness of breath
☐Rapid breathing
☐Recurrent colds
☐Coughing up blood
☐Ankle swelling
☐Palpitations
☐Rapid or irregular pulse
☐Chest pain
☐High blood pressure
☐Low blood pressure
☐Headache
☐Neck pain or stiffness
☐Sore throat
☐Blurry vision
☐Double vision
☐Sensitivity to light
☐Seeing spots or shadows
☐Hearing loss
☐Ringing in the ears
☐Disturbance in sense of smell
☐Runny nose
☐Dry mouth
☐Sore tongue
☐Difficulty swollowing
☐Nausea or vomiting
☐Abdominal pain
☐Constipation
☐Diarrhea
☐Loss of bowel control
☐Frequent belching or gas
☐Vomiting blood
☐Bloody (red or black) stools
☐Yellowing of the skin
☐Back pain or stiffness
☐Joint pain or stiffness
☐Bone pain
☐Muscle pain
☐Muscle cramps

☐Dry hair
☐Dry skin
☐Hair loss
☐Easy bruising
☐Sun sensitivity
☐Rash
☐Itching
☐Painful urination
☐Difficulty starting urination
☐Loss of bladder control
☐Urine with unusual odor
☐Cloudy urine
☐Blood in urine
☐Decreased sexual desire

Women

☐No menses
☐Irregular menses
☐Painful periods
☐Heavy periods
☐Abnormal vaginal bleeding
☐Abnormal vaginal discharge
☐Painful intercourse (sex)

Men

☐Inability to have an erection
☐Inability to maintain an erection
☐Inability to ejaculate (orgasm)
☐Delayed ejaculation
☐Early ejaculation
☐Scrotal pain
☐Abnormal penis discharge

☐Other

Explain: _____
_____
_____
_____
_____
_____
_____

APPENDIX I. Authorization to release medical information

UNIVERSITY of ROCHESTER MEDICAL CENTER
& Affiliates

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Strong Memorial Hospital
Department or Practice _____
601 Elmwood Avenue, Box #: _____
Rochester, NY 14642
Phone: (585) _____ Fax: (585) _____

SH 48 Authorization for Release/Disclosure of Medical and/or Behavioral Health Information

RR DONNELLEY

PLEASE PRINT:
Patient name: _____ Date of Birth: _____
Address: _____ Patient's phone#: ( ) _____
City/State/Zip: _____

This Authorization allows URMC & Affiliates to: (check one or both)

☐ **SEND** copies of your record to (or discuss your information with) the provider/person/facility below

☐ **RECEIVE** copies of your record from (or discuss your information with) the provider/person/facility below

Name of Provider/ Person/Facility _____ Address _____

City, State, Zip Code _____ Phone #/Fax # (include area code) _____

PURPOSE FOR THIS REQUEST: ☐ Healthcare or Appointment **(date)** _____ ☐ Insurance ☐ Other

TYPE OF RECORDS or INFORMATION REQUESTED: Check all that apply:

The records requested are to include: ☐ Mental Health Treatment Records ☐ Alcohol/Drug Treatment Records
(Release/disclosure of HIV-related information requires additional authorization on form NYS DOH2557 or OCA 960)

☐ **Inpatient admission(s)/date(s):** _____
(Check only **one** of the following 3 choices if requesting inpatient records)
- ☐ Treatment summary (includes discharge summary, history/physical, laboratory tests, x-ray reports, operative reports, pathology)
- ☐ Specific information or reports (describe): _____
- ☐ Other (describe): _____

☐ **Outpatient/Office visits--date(s):** _____ **and/or specific illness/injury:** _____.
(Check type of outpatient visit to be released)
☐ Clinic/doctor/dental visit ☐ Ambulatory Surgery visit ☐ Emergency Department Record
☐ Radiology report(s) ☐ Laboratory test results ☐ Immunizations ☐ Physical/occupational therapy record(s)
☐ Other (describe): _____

AUTHORIZATION VALID FOR: (If nothing is checked below, this authorization is valid for this request only.)
☐ This request only
☐ One year from the date of this authorization **OR** _____ (insert date). This authorization applies to the records of the treatment received on or prior to the date of this authorization.
☐ This request **and** for medical records of any **future** treatment of the type described above until: _____(insert date)

I understand that:
- My right to healthcare treatment is not conditioned on this authorization, except in very limited circumstances (e.g. non-emergent mental health or chemical dependency treatment).
- I may cancel this authorization at any time by submitting a *written* request to the address provided at the top of this form, except where a disclosure has already been made in reliance on my prior authorization.
- If the person or facility receiving this information is not a health care or medical insurance provider covered by privacy regulations, the information stated above could be redisclosed, except that chemical dependency treatment records protected by Federal Confidentiality Rules 42CFR Part 2 may not be disclosed without my written authorization unless otherwise provided for in the regulations.
- There may be a charge for the requested records.
- The medical records requested above may be faxed in cases of medical necessity.

Signature of Patient or Representative _____ Date _____

Relationship to Patient *(if Representative)* _____

Revised 8/11 *Distribution:* Original to medical record. Copy to patient as required.

This authorization must be retained for a minimum of six years beyond the validation limits.

APPENDIX J. List of study personnel

Principal Investigator

Bogachan Sahin, MD, PhD
Assistant Professor, Department of Neurology

Co-Principal Investigators

Bradford Mahon, PhD
Assistant Professor, Departments of Brain and Cognitive Science and Neurosurgery

Zoe Williams, MD
Associate Professor, Department of Ophthalmology

Sub-Investigators

Curtis Benesch, MD, MPH
Professor, Department of Neurology

Jeffrey Burdett, MD
Assistant Professor, Department of Neurology

Ania Busza, MD, PhD
Experimental Therapeutics Fellow, Department of Neurology

Michael Chilungu, MD
Assistant Professor, Department of Neurology

Fulvio Gil, MD
Vascular Neurology Fellow, Department of Neurology

Todd Holmquist, MD
Assistant Professor, Department of Neurology

Adam Kelly, MD
Associate Professor, Department of Neurology

Anthony Noto, MD
Vascular Neurology Fellow, Department of Neurology

Study Coordinator

Ann Leonhardt, NP
Research Coordinator, Department of Neurology