CLINICAL RESEARCH PROTOCOL

FLOW TRIAL:
FLUOXETINE to OPEN the CRITICAL PERIOD TIME WINDOW TO IMPROVE MOTOR RECOVERY AFTER STROKE

Protocol Version 1.9, November 21, 2017

Funding/Sponsors:
Brain Canada, and
Heart and Stroke Foundation Canadian Partnership for Stroke Recovery

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INVESTIGATOR AGREEMENT

FLOW trial: Fluoxetine to open the critical period time window to improve motor recovery after stroke

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I have read the protocol and agree that it contains all necessary details for carrying out this trial. I undertake to conduct this trial within the time designated.

I understand that all participant information in connection with this trial is considered confidential information.

The information includes clinical protocol, the Case Report Form, technical methodology and basic scientific data.

By my signature below, I hereby attest that I have read, understood and agree to abide by all conditions, instructions and restrictions contained in the above protocol.

Investigator:

Name	Signature	Date
_____	_____	_____

Name and Address of Investigational Site:

_____
_____
_____
_____

SIGNATURE PAGE FOR SPONSOR

Title: ***FLOW trial: Fluoxetine to open the critical period time window to improve motor recovery after stroke***

Protocol Version: 1.9 November 21, 2017

Approved by the following:

_____ _____

Dr. Mark Bayley Signature Date

Protocol Version Record

Version	Amendment	Date
V0.1	Initial Draft Version	18-December-2015
V0.2	First Update	12-February-2016
V0.3	Update	22-February-2016
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V1.8	Update with Blood Draw Details	25-October-2017
V1.9	Update	21-November-2017

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Quick Protocol Synopsis

Title: FLOW Trial: Fluoxetine to Open the Critical Period Time Window to Improve Motor Recovery after Stroke

Study Design

This multi-year trial aims to recruit 176 stroke patients across multiple (5-10) sites in Canada. Half of the participants will be given fluoxetine (Prozac) while the other half will be given placebo. All participants will undergo a 12-week structured exercise program while they are on drug/placebo. All study participants will undergo evaluation at baseline, immediately following the exercise program, and 6 months post-intervention.

Study Population

Study participants must meet the inclusion/exclusion criteria at the time of entry into the study. In general, participants will be classified as moderate-to-severe stroke, as defined in the inclusion/exclusion criteria, at the time of entry into the study, even though they may have been initially defined outside of the criteria at the point of screening.

Study Rationale

Fluoxetine has been shown in animal models to keep open the period of neuroplasticity that follows a stroke (which also coincides with recovery) and the rationale is that by pairing fluoxetine with exercise/rehab in humans that motor function will be significantly improved.

Objectives

Primary Objective

- test whether fluoxetine (Prozac) can enhance the effects of exercise/rehabilitation on lower limb motor function following stroke.

Secondary Objectives

- investigate the effects of fluoxetine (Prozac) and exercise on other domains including but not limited to: balance and mobility, cognition, mood, functional status, and quality of life.
- examine the associations related to biomarkers including blood/saliva, brain imaging, and heart and other physiological biomarkers obtained using monitoring equipment such as heart monitors and activity accelerometers.
- set up the infrastructure and expertise for a national clinical trials platform for stroke rehabilitation across Canada for future clinical trials.

Background and Rationale

Improving upper and lower extremity mobility is one of the top priorities agreed upon by stroke survivors, caregivers and health professionals (Pollock 2014). After a stroke, two thirds of survivors will achieve independent but usually slow and inefficient ambulation, while less than half will recover upper limb function at six months (Kwah 2013). Walking ability has important implications after stroke. Patients with poor walking ability are more likely to be discharged to nursing homes following a stroke (Portelli 2005) and have an increased probability of death (Wade 1984).

Findings in the last 15-20 years suggest that stroke and related injuries create a cerebral milieu similar to that of early brain development in childhood, a period characterized by rapid neuronal growth and neuroplasticity. In the first weeks following stroke there is a period of increased expression of growth factors and genes important for dendritic growth, formation of new neural connections and blood vessels (Murphy 2009). Animal and human studies have shown that rehabilitation is most effective during this time window but this "critical period" begins to close after 1-3 months, coinciding with plateaus in behavioural recovery (Biernaskie 2004; Murphy 2009; Krakauer 2012). New findings suggest that it may be possible to reopen or extend this critical period and thereby markedly increase the level of functional recovery. The FLOW Trial aims to keep open or re-open the "recovery window" for those affected by stroke, increasing the recovery potential for people two to seven months post-stroke using the drug fluoxetine (Prozac) in combination with exercise. If successful, people may be able to achieve significant gains through rehabilitation at a time when they typically "plateau" in their recovery, and thus potentially dramatically change outcomes for Canadians living with stroke.

Fluoxetine may offer enhanced motor recovery after a stroke

There has been increasing interest in the use of pharmacological interventions to enhance recovery after a stroke. The FLAME randomized controlled trial (RCT) (Chollet 2011) produced some of the first definitive results for recovery-enhancing effects of fluoxetine, an antidepressant of the selective serotonin reuptake inhibitor (SSRI) class. Provided to non-depressed patients from 5-10 days post-stroke for 90 days, fluoxetine resulted in improved motor scores, as well as a greater proportion of patients who reached a good recovery as indicated by a modified Rankin Score (mRS) of 0 to 2. Replication of the FLAME trial is now underway with the Australian Affinity Trial (1600 patients) and UK FOCUS trial (3000 patients). The positive effects may be due to a number of mechanisms demonstrated in animal models including a decrease in inflammatory factors, increase in survival of injured cortical neurons, an increase of neurotrophic factors, as well as an increase in neurogenesis (Dhami 2013; Espinera 2013). The FLAME and ongoing trials of fluoxetine address the acute recovery phase as there is strong evidence from the animal literature that there is a window of time when optimal responses can be attained after a stroke, and that delays may be detrimental to neurological recovery (Krakauer 2012). The

Copenhagen Stroke Study (over 1000 patients) demonstrated that the greatest human neurological recovery occurred within 4.5 weeks of the stroke event in 80% of the patients, while the largest gains in function were achieved by 6 weeks (Jørgensen 1995). However, there is some compelling indication that SSRIs may have application in more chronic conditions. A single SSRI dose has been shown to increase muscle activation (Berends 2009), as well as dexterity (Zittel 2008) in chronic stroke patients. An intervention that could be utilized with chronic stroke could potentially reach more than 300,000 people living with stroke in Canada.

Early in life, there are time-limited periods of heightened brain plasticity when neural circuits can be readily modified by experience. These periods are called "critical periods" such as those that occur in the visual cortex. Once these critical periods are over, neural circuitry becomes resistant to change. Interestingly, the closure of critical periods in different mammalian sensory and motor systems coincides with the formation of growth-inhibitory perineuronal nets (PNNs) that form around many cortical neurons (Wang 2012). Disruption of PNNs in adult animals with different drugs, including fluoxetine, reinstates "juvenile" levels of neuroplasticity normally restricted to the critical periods of early brain development (Pizzorusso 2002; Maya Vetencourt 2008; Kobayashi 2010). Following spinal cord injury or stroke in animals, disruption of PNNs with fluoxetine or other agents results in sprouting of new connections both around and distal to the site of injury and this response is associated with improved functional recovery (Bradbury 2002; Soleman 2012; Scali 2013). Thus, by reducing plasticity-limiting PNN formation with fluoxetine it may be possible to reopen the critical period for stroke recovery in many patients whose recovery has plateaued. There appears to be preliminary evidence that SSRIs function optimally to improve motor function when provided in conjunction with motor practice or exercise. For example, Zittel et al. (2008) found that a single dose of SSRIs improved dexterity only after an hour exercise practice session.

Overall Study Objectives

While a number of ongoing trials are positioned to replicate and increase the generalizability of the FLAME study, our proposed trial will address a *different* population of patients (i.e., 2-7 months post-stroke) using a *combination intervention* in which we attempt to re-open the critical period of heightened plasticity for stroke recovery. We will assess whether fluoxetine (Prozac), by increasing neuroplasticity, enhances the effects of exercise/rehabilitation on motor function? Specifically, we will undertake a double-blind randomized controlled trial to determine whether a 3-month course of fluoxetine (Prozac) enhances the effects of task-specific exercise on motor function in patients two to seven months post-stroke.

Primary Objective

The primary objective is to test whether fluoxetine (Prozac) can enhance the effects of exercise rehabilitation on motor function following stroke.

Primary Outcome

The primary outcome will be lower limb motor function as measured by the Fugl-Meyer leg score.

Primary Hypothesis

Our primary hypothesis is that the group receiving fluoxetine (Prozac) coupled with task-specific exercise rehabilitation will have significantly higher Fugl-Meyer leg scores as compared to the group who receive a placebo coupled with task-specific exercise rehabilitation.

Secondary Objectives

Secondary objectives include investigating the effects of fluoxetine (Prozac) and exercise on other domains including but not limited to: balance and mobility, cognition, mood, functional status, and quality of life. Secondary objectives will also include examining the associations related to biomarkers including blood and/or saliva/cheek swabs, brain imaging, and heart and other physiological biomarkers obtained using monitoring equipment such as heart monitors and activity accelerometers.

In addition, a significant outcome from the FLOW trial will be the experienced networked infrastructure that will become a national stroke clinical trials platform across Canada. By gaining expertise in coordinating studies that require recruitment strategies for consecutive patient sampling, rigorous evaluation, quantification of concurrent exercise, and collection and analysis of serum biomarkers related to recovery, the national platform will be ready to support other novel interventions in the future.

Trial Design

FLOW Trial is a randomized, placebo-controlled, blinded phase 2 trial evaluating the efficacy of coupling antidepressant therapy (e.g., SSRI fluoxetine (Prozac)) with task-specific exercise rehabilitation across multiple Canadian sites in 176 stroke patients. 88 patients will be enrolled in each arm of the study. Both groups will receive an intense task-specific exercise program in addition to standard of care rehabilitation, but only one group (the intervention group) will receive the active drug fluoxetine (Prozac). The reason is that it is already well documented that adding an intense exercise program will improve recovery and thus no ethical or scientific purpose for having a true negative (no treatment) control group.

Study participants will be evaluated at baseline, immediately following exercise program and 6-months post-intervention. Evaluators and participants will be blind to the treatment administered. Trial is constructed with randomization to remove selection and allocation biases and to ensure greater validity in observed differences in the outcome measures. The Applied Health Research Centre (AHRC) will act as the coordinating and analysis center. Marchese Health Care will be manufacturing and providing the study medication, and responsible for participant group randomization.

Trial Sites

Trial will be conducted at participating rehabilitation sites across Canada (approximately 5-10 sites in total).

Participant Selection

FLOW Trial plans to enroll 176 participants over two years. Potential participants will be identified by the multidisciplinary team caring for the patient and referred to the study team. Patients that consent to participating in the study will be enrolled within 60 to 210 days of an acute ischemic stroke. While no specific stratification will be imposed, there is intent to split groups into early (60 to 120 days) and late (121 to 210 days) subgroups for subgroup secondary analyses.

Inclusion Criteria

1. 25 years of age or older
2. Days post stroke must be between 60 – 210 days when enrolled
3. Measureable hemiparesis at enrolment with a lower limb Fugl-Meyer score $\leq$ 30

Exclusion Criteria

1. Patients with subarachnoid hemorrhage
2. Pre-morbid modified Rankin score > 2
3. Substantial premorbid disability or pre-existing deficit or language comprehension deficit that could interfere with assessments
4. Diagnosis of major depressive disorder/anxiety disorder requiring antidepressant use within 6 weeks of enrolment
5. Taking neuroleptic drugs, benzodiazepines, monoamine oxidase inhibitors within 30 days of enrolment
6. Unstable serious medical condition (e.g., terminal cancer, renal or liver failure, congestive heart failure)
7. Resting blood pressure exceeding 180/100mmHg
8. Requires more than a one person assist for transfer
9. Planned surgery that would affect participation in the trial
10. Participating in another exercise program more than one day per week
11. Cannot be pregnant
12. Patients with an ongoing history of illicit drug use and/or alcohol abuse
13. Patient unwilling or unable to comply with trial requirements

14. Patient unable to understand English

Study Procedures

Screening and Consent

The trial will be explained and consent obtained for participation from the patient or his/her substitute decision maker. Inclusion and exclusion criteria will be assessed by reviewing the patient's medical history. Following screening, eligible patients will be enrolled and proceed to baseline evaluation.

Baseline Evaluation

Once enrolled, participants will undergo baseline evaluation within four weeks of screening. Baseline assessments will evaluate physical, functional, and cognitive functioning, as well as level of impairment. Total time to complete baseline study assessments is estimated at 2-3 hours, and may be completed over multiple visits, if necessary. MR imaging with a research protocol will be obtained (or if unavailable, a copy of the patient's clinical CT or MR brain imaging will be obtained). Participants will also be sent to a clinical laboratory for blood collection and analysis (if blood collection is not possible, saliva or cheek swap samples will be taken for genetic testing).

Therapeutic Protocol

Trial Drug Commencement

Following enrolment and baseline evaluation (up to four weeks later), the participant will be randomized into the fluoxetine (Prozac) or placebo group. Randomization will be controlled by the trial pharmacist (Marchese Health Care). The trial pharmacist will prepare the drug capsules which will be either 10mg or 20mg fluoxetine (Prozac), or 0mg placebo capsules. The active drug capsule will be over-encapsulated to appear identical to the placebo capsule in appearance and packaging. Based on recent evidence that a permissive environment must first be created to prime the brain prior to intensive therapy to restore motor function (Wahl 2014), following initiation of the drug, participants will undergo an accommodation period (approximately 3-5 weeks) to ramp up from an initial daily dose of 10mg to a final daily dose of 20 mg drug prior to commencing the exercise program. Participants will receive telephone follow-up calls to ensure compliance during the ramp-up period. Following the ramp-up period, participants will continue on the trial drug (fluoxetine (Prozac) or placebo) for a period of at least twelve weeks, until completion of the exercise program.

Task-Specific Exercise Program

Following the drug accommodation period, both groups will be asked to participate in a 60-minute exercise program (approximately 3 times per week for 12 weeks). As there is prior evidence that fluoxetine increases muscle activation after stroke (Berends et al. 2009), exercises will focus on muscle strengthening

of the lower extremities, and repetitive tasks to transfer changes in muscle to functional outcomes, including walking. This exercise will take place at a mild to moderate intensity as such exercise intensity has been shown to enhance expression of brain-derived neurotrophic factor (BDNF) (Leckie et al. 2014).

Sessions will likely take place in the outpatient department of a rehabilitation centre due to the need for specialized rehabilitation equipment (treadmill, weights) and will be supervised in small groups (e.g., 1:1-3) by a physical therapist, preferably with experience with stroke. The exercise program will challenge muscle strengthening through single joint graded exercises (e.g., using theraband or weights) and multi-joint task-specific motor activities utilizing the lower extremities (e.g., rise from chair). Balance and walking tasks will be utilized to enable transfer of strength gains to real-world mobility functions. As we expect varying motor ability among the participants, exercises will be customized to the abilities of participants, and gradually increased in intensity over the sessions depending on the tolerance of the participant. Participants will be queried on any lasting fatigue, pain and muscle soreness at the beginning of each session, and the intensity will be adjusted as appropriate. The progression will be documented and replicable. Multiple methods of monitoring exertion will be undertaken, including the Borg Rating of Exertion (encouraging maximum exertion of somewhat hard or 13/14 on the 20 point scale) and heart rate monitoring (encouraged to keep heart rate below the maximum 60% heart rate reserve and average of 50% heart rate reserve over the session). Heart rate monitors and step counters will be worn during all sessions, where possible, to ensure that the exertion and repetition targets are met and enable quantifiable progression. Our team has undertaken similar exercise protocols in people with stroke, including an 11-site multi-site study undertaken in community centres (Mayo et al. 2015).

Post-Exercise Evaluation

Within four weeks of completing the exercise program, participants will undergo a post-exercise evaluation. By this time, participants will have ceased taking trial medication (fluoxetine (Prozac) or placebo) as part of the trial. Post-exercise assessments will evaluate physical, functional, and cognitive functioning, as well as level of impairment. Time to complete post-exercise study assessments is estimated at 2 hours. Participants will also be sent to a clinical laboratory for blood collection and analysis.

Post-Exercise Evaluation

At 6-months post-exercise program (± four weeks), participants will undergo a six-month follow-up evaluation. Follow-up assessments will evaluate physical, functional, and cognitive functioning, as well as level of impairment. Time to complete post-exercise study assessments is estimated at 2 hours. Participants will also be sent to a clinical laboratory for blood collection and analysis.

List of Study Assessments and Biomarkers

Name of Assessment / Biomarker	Time to administer	Visits to Administer
GENERAL (1 minute to administer at baseline only)		
1) Bryden Handedness Questionnaire	*1 min*	Baseline
PHYSICAL MEASUREMENTS (40 minutes to administer at each visit not including any set up time required)		
2) 6 Minute Walk Test / 10 Meter Walk Test	*10 min*	Baseline, Post-Exercise, 6-mo
3) Knee Extensor Strength & Velocity tests	*5 min*	Baseline, Post-Exercise, 6-mo
4) Berg Balance assessment	*15 min*	Baseline, Post-Exercise, 6-mo
5) Grip Strength	*5 min*	Baseline, Post-Exercise, 6-mo
6) Waist-to-hip ratio	*2 min*	Baseline, Post-Exercise, 6-mo
7) Body Mass Index	*3 min*	Baseline, Post-Exercise, 6-mo
FUNCTIONAL MEASURES (15 minutes to administer at each visit plus an extra 7 min at baseline)		
8) Modified Rankin Score	*5 min*	Baseline
9) Functional Comorbidity Index Scale	*2 min*	Baseline
10) Stroke Impact Scale (SIS)	*15 min*	Baseline, Post-Exercise, 6-mo
IMPAIRMENT MEASURES (30 minutes to administer at each visit plus an extra 10 min at baseline)		
11) Fugl-Meyer motor score (arm & leg)	*30 min*	Baseline, Post-Exercise, 6-mo
12) NIH Stroke Severity scale	*10 min*	Baseline
DEPRESSION MEASURES (10 minutes to administer)		
13) PHQ-9	*10 min*	Baseline, Post-Exercise, 6-mo
COGNITIVE MEASURES (25 minutes to administer at each visit plus an extra 2 min at baseline)		
14) Simple and Choice Reaction Time tests	*5 min*	Baseline, Post-Exercise, 6-mo
15) Trail Making Test – A & B	*5 min*	Baseline, Post-Exercise, 6-mo
16) MOCA (including 5 word recall and clock test)	*15 min*	Baseline, Post-Exercise, 6-mo
17) Line Bisection Task	*2 min*	Baseline
BIOLOGICAL BIOMARKERS		
18) Fasting Blood Draws – taken separately at a local lab		Baseline, Post-Exercise, 6-mo
Saliva or Cheek Swab Samples (taken if blood draw is not possible at baseline)		Baseline
BRAIN IMAGING BIOMARKERS		
19) MRI scan using a research protocol (if unable, a copy of clinical CT or MRI scan will be obtained, if available)		Baseline

Summary of administration times: 125 minutes at each visit, plus an additional 20 minutes at baseline.

MRI Scans
Raw MR images will be housed in a central database for processing by the Brain Imaging Processing lab at Sunnybrook (Dr. S. Black) and will be available for secondary analysis investigations.

Blood Analyses
Blood samples will be analyzed to measure levels of HbA1c (a measure of long-term glucose levels), cholesterol (specifically triglycerides, high and low density lipoproteins), inflammatory markers (C-reactive protein), homocysteine, and various cytokines (specifically interleukin 6 and 10). Blood (or saliva/cheek swab samples) will undergo genetic testing of protein coding genes (apolipoprotein E - ApoE) and neuronal growth genes (brain-derived neurotrophic factor - BDNF).

In addition, unused blood samples will be processed and centrally stored in cryovials in a minus 80 degrees freezer for future analyses under the supervision of Study Investigator, Dr. Sandra Black (Sunnybrook, M6 West, 2075 Bayview Avenue, Toronto). The intent is to make the stored frozen cryovials available to all CPSR investigators to apply for access. Access will be controlled by a Subcommittee of CPSR Investigators who will review and approve requests and oversee access to the biobank. Stored cryovials will remain at Sunnybrook under the supervision of Dr. Sandra Black for a period of up to 10 years. If required, disposal of human blood and blood products will be done by placing the samples in specially designated plastic sharps containers to be removed and disposed of by environmental services in accordance with Sunnybrook policies.

Time and Events Schedule

Visit	1	2	3	4	5	6
Timing	Screen	Baseline	Drug/Placebo Start (approx. 3-5 weeks in duration)	Exercise Program (12 weeks in duration (±1 week)	Post-Exercise Program Follow-up	Six-Month Post-Exercise Program Follow-up
Study Day	1					
Visit Window (±weeks)		up to 4 weeks after screen	up to 4 weeks after baseline	3-5 weeks after starting Drug/Placebo	up to 4 weeks after completing intervention	±4 weeks around six months follow-up
STUDY PROCEDURES						
Informed Consent	X					
Inclusion/Exclusion	X	X				
Demographics	X					
Medical/Surgical History	X					
Concomitant Meds	X	X	X	X	X	X
Vital Signs	X	X	X	X	X	X
SAE Assessments		X	X	X	X	X
ASSESSMENTS						
Assessments – List		X			X	X
BIOLOGICAL BIOMARKERS						
Fasting Blood Samples / (Saliva/Cheek Swab Samples if needed)		X			X	X
BRAIN IMAGING BIOMARKERS						
Research MRI scans (or copy of Clinical CT or MRI Scan)		X				

Statistical Analysis

Using data from the LEAPs trial (Nadeau 2013), a change between 1.3-2.5 points on the Fugl-Meyer Lower Extremity (FM-LE) is expected with exercise alone commenced between 2 and 4 months, although the changes are less (1.3-1.5) when commenced later (4 months). Using data from the FLAME trial (Chollet 2011), an additional 2 point change on FM-LE (total 4) may be achieved at 90 days in the group taking fluoxetine (as compared to the control group receiving placebo). To estimate sample size needed, we estimated a between group difference of 4 points on the FM-LE, with a standard deviation of 8, 80% power and a conservative baseline to post correlation of 0.75. With these estimates, 71 subjects per group (total 142) are required. Accounting for an additional 15-20% drop-out, we will recruit a total of 176 subjects. Estimates of the effect of the experimental intervention on the primary endpoint (FM-LE) will be determined using an analysis of covariance which is a method superior to change score and repeated measures analyses (Van Breukelan 2006; Vickers 2005). We will utilize intention-to-treat principles and multiple imputation techniques will be used for missing data. Secondary outcomes, as well as the follow-up time-point (6-months after intervention ends) will utilize the same analyses (analysis of covariance).

Participant Withdrawal

Participants may withdraw from the trial for any of the following reasons:

- Participant or caregiver withdraws further participation in trial for any reason
- Participant becomes unable to continue taking trial medication (e.g., unable to tolerate 20mg dose), complete trial exercise program, and/or complete trial visits
- Any medical condition that, in the opinion of the PI, may jeopardize the participant's safety if they continue in the trial

Serious Adverse Events

Handling of Serious Adverse Events (AEs)

Site qualified investigators will be responsible for appropriate medical care of participants during the study, in connection with trial procedures and assessments, and for monitoring the safety of participants. The overall PI will provide medical monitoring to all sites, and he, or his physician designee, will be available 24 hours a day for protocol questions, violations, and serious adverse events.

Definition of an Adverse Event

An adverse event (AE) is an untoward medical occurrence in a participant that occurs during the course of the clinical trial which may or may not have a causal relationship with the trial procedures. An AE can be any unfavourable or unintended sign (e.g., abnormal laboratory finding), symptom, or disease temporally associated with a trial procedure.

Serious Adverse Events

A serious adverse event (SAE) is defined as an AE that results in any of the following outcomes:

- Death
- Life-threatening situation (participant was in immediate risk of death at the time of the event. However, an event that might have hypothetically caused death if it was of greater severity is not included.)
- New in-patient hospitalization or prolongation of existing hospitalization
- Persistent or significant disability or incapacity
- Important medical events not resulting in death, be life-threatening, or requiring hospitalization but may jeopardize the participant and may require medical or surgical intervention to prevent one of the above outcomes (based upon appropriate medical judgment)

All SAEs will be assessed during the course of the trial, and the delegated study clinician who examines and evaluates the participant will determine the event's causality to the trial's procedures, based on temporal relationship and his/her

clinical judgment. **It is the responsibility of the site QI to ensure all SAEs are assessed to determine causality, that is, to determine the likelihood that the SAE was caused by a study intervention.**

Degree of certainty about causality will be graded as follows:

- **Definitely Related:** Clear evidence to suggest a causal relationship and other possible contributing factors can be ruled out.
- **Probably Related:** Evidence to suggest a causal relationship and the influence of other factors is unlikely.
- **Possibly Related:** Some evidence to suggest a causal relationship but the influence of other factors may have contributed to the event.
- **Unlikely:** The temporal relationship to the trial procedures makes a causal relationship improbable and/or the SAE is more likely due to other factors such as concomitant medication(s) or concomitant disease(s).
- **Not related:** The SAE is completely independent of trial procedures, and/or evidence exists that the event is definitely related to another etiology.

Documenting Serious Adverse Events

Pre-existing conditions will be recorded at the baseline visit following participant enrolment (including start date of the condition, frequency, and severity). After the participant signs the informed consent form, any worsening of these conditions will be documented.

SAEs experienced by the participant between the signing of the Informed Consent and 30 days after completion of the final follow-up appointment (the six months post completion of the exercise program visit) will be recorded in the electronic case report form (eCRF)

Following up on Adverse Events

The site qualified investigator is obliged to follow participants with AEs until the events have subsided, the conditions are considered medically stable, the investigator considers it medically justifiable to terminate follow-up, or the participants are no longer available for follow up. Participants who discontinue due to adverse events will be treated and followed according to established medical practice. All pertinent information will be entered into the eCRF.

All SAEs should be monitored until resolved or until the SAE is clearly determined to be due to a participant's stable or chronic condition or intercurrent illness(es).

Reporting Serious Adverse Events

All SAEs which occur during the course of the study visits or within 30 days of the post-exercise program study visit will be reported to the study Coordinating Centre within one working day of site personnel being notified of the occurrence of the event.

SAEs will be reported directly on the eCRF within 24 hours of becoming aware of the event, and update as additional information becomes known. The initial SAE report should include at a minimum: subject number, a narrative description of the event, and an assessment by the qualified investigator (or designee) of the intensity of the event and relationship of the event to trial procedure. The initial SAE report received from the site should be completed as soon as possible. A complete follow-up SAE report must be submitted when information not available at the time of the initial report becomes available. Sites can refer to the Data Entry Guidelines for instructions on accessing the eCRF.

The Coordinating Centre personnel will process SAE reports as per the SAE Reporting Guidelines. All SAEs will be reviewed by the Medical Monitor who will determine whether criteria for expedited reporting to Health Canada have been met. Health Canada reportable SAEs will be distributed to sites. Sites will report SAEs and Safety Reports to their REB as per local requirements.

Data Collection and Methodology

The Coordinating Centre (CC) will serve as the central data collection site for this multi-center study. All eligible participants will be registered with the central data collection center prior to the initiation of any portion of the experimental therapy. The staff at the CC will review the baseline data and ensure that the participant meets the eligibility criteria and has provided informed consent. The CC will be responsible for collection, collating and analyzing the data collected by this study. The investigator or his delegate will record data on the electronic Case Report Forms (eCRF) provided by the CC. Data will be managed in accordance with the good clinical practices (GCP) for research trials involving human subjects.

Data Safety Monitoring Board

A Data Safety Monitoring Board will oversee the trial. The DMSB will be made up of people with expertise in trial monitoring. They will be responsible for monitoring patient safety, trial progress, and patient recruitment. In addition to providing study advice, the DSMB will be consulted for team conflicts and unresolvable issues.

Quality Assurance

All centers participating in the study may be subjected to an audit of their data. At the time of the audit, all records requested must be provided to the auditors.

Confidentiality and Subject Data Protection

The participants will be informed that data will be stored and analyzed by computer. The data will be stripped of participant identifiers prior to storage. All participant information will be kept confidential and the participant will not be recognizable in data submitted for publication.

Publications

The results and experiences derived from this study will be jointly published by the investigators in the appropriate medical journals. Ad-hoc writing committees will be defined for writing and reviewing each publication. The support of the Heart and Stroke Foundation Canadian Partnership for Stroke Recovery (CPSR), and Brain Canada Foundation will be recognized in all publications that result from this study.

Ethics and Informed Consent

This trial will be conducted in accordance with the current version of the *Tri-Council Policy Statement: Ethical Conduct for Research Involving Humans.*

Subject information, informed consent, and confidentiality

Prior to entry in the trial, the investigator will explain to potential participants reasonably anticipated benefits and potential hazards of the trial and any discomfort it may entail. Participants will be informed that they are at liberty to abstain from participation in the trial and are free to withdraw consent to participate at any time. They will be told which alternative treatments are available if they refuse to take part and that such refusal will not prejudice future treatment. Finally, they will be told that competent authorities may examine their records and authorized persons but that personal information will be treated as strictly confidential and will not be publicly available. Participants will be given the opportunity to ask questions. After this explanation and before entry to the trial, consent should be appropriately recorded by means of the subject's dated signature.

Protocol Reviews

The study will not start until approval of the protocol by the appropriate Institutional Ethics Review Board (IRB). It is the responsibility of the Investigator to keep the Institutional Review Board and the Study Safety Committee informed of any Serious Adverse Events and amendments to the protocol. Annual re-approval will be required for as long as the study is open to patient accrual.

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