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# Trial of Remote Ischaemic Pre-Conditioning in Vascular Cognitive Impairment (TRIC-VCI): Protocol for a randomised controlled trial



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# Trial of Remote Ischaemic Pre-Conditioning in Vascular Cognitive Impairment (TRIC-VCI): Protocol for a randomised controlled trial

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## ABSTRACT

**Introduction:** Cerebral small vessel disease (cSVD) accounts for 20-25% of strokes and is the commonest cause of vascular cognitive impairment (VCI). In an animal VCI model, inducing brief periods of limb ischaemia-reperfusion reduces subsequent ischaemic brain injury with remote and local protective effects, with hindlimb remote ischaemic conditioning (RIC) improving cerebral blood flow, decreasing white-matter injury, and improving cognition. Small human trials suggest RIC is safe and may prevent recurrent strokes. It remains unclear what doses of chronic daily RIC are tolerable and safe, whether effects persist after treatment cessation, and what parameters are optimal for treatment response.

**Methods and Analysis:** This prospective, open-label, randomised controlled trial (RCT) with blinded endpoint assessment and run-in period, will recruit twenty-four participants, randomised to one of two RIC intensity groups: one arm treated once daily or one arm twice daily for 30 consecutive days. RIC will consistent of 4 cycles of blood-pressure (BP) cuff inflation to 200 mmHg for 5-minutes followed by 5-minutes deflation (total 35-minutes). Selection criteria include:age 60-85, evidence of cSVD on brain CT/MRI, Montreal Cognitive Assessment (MoCA) score 13-24, and preserved basic activities of living. Outcomes will be assessed at 30-days and 90-days (60-days after ceasing treatment). The primary outcome is adherence (completing ≥80% of sessions). Secondary safety/tolerability outcomes include the percent of sessions completed and pain/discomfort scores from patient diaries. Efficacy outcomes include changes in cerebral blood flow (per arterial spin-label MRI), white-matter hyperintensity volume, diffusion tensor imaging, MoCA and Trail-Making tests.

**Ethics and Dissemination:** Research Ethics Board approval has been obtained. The results will provide information on feasibility, dose, adherence, tolerability, and outcome measures that will help design a phase 2b RCT of RIC, with the potential to prevent VCI. Results will be disseminated through peer-reviewed publications, organisations and meetings.

**Registration Details:** NCT04109963; Pre-results

## ARTICLE SUMMARY

### Strengths and limitations of this study

- This trial will enrol patients using established neuroimaging criteria for the diagnosis of cerebral small vessel disease (cSVD), ensuring a valid sample of the target condition.
- Patients will be enrolled into two active comparator groups of remote ischemic pre-conditioning (RIC), with the primary goal of comparing the tolerability of different doses.
- The use of intent-to-treat analysis, pre-specified primary and secondary outcomes, and candidate biomarkers for monitoring treatment response will improve upon previous small studies of remote ischaemic pre-conditioning in cSVD; however, the lack of a non-treated control group means that only within-patient changes can be analyzed.
- The use of a 60-day wash-out period after 30-days of treatment will help clarify the persistence of any RIC-related treatment effects.
- Participants and healthcare providers will not be blinded to the intervention, but endpoint assessment will be blinded to treatment allocation.

## INTRODUCTION

Cerebral small vessel disease (cSVD) is the commonest cause of vascular cognitive impairment (VCI), accounting for about 30% of all cases of dementia in community-based neuropathological studies.[1-3] cSVD can be identified on magnetic resonance imaging (MRI) using markers like small subcortical infarcts, lacunes, and white matter hyperintensities (WMHs).[2] cSVD patients have frequent, small brain infarcts, making this an ideal condition to study an intervention to condition the brain to resist ischaemia.[4 5] Although each new infarct is insidious and may not have an easily identified acute presentation, over time the cumulative burden of ischaemic damage leads to accelerated cognitive decline.[6 7] There are no proven therapies for preventing cSVD progression.[8] Strategies that can be safely applied early in the disease course would be particularly desirable.[9]

Experimentally inducing brief periods of ischaemia-reperfusion that do not result in tissue injury before an ischaemic event can reduce subsequent injury.[10] This process, known as ischaemic preconditioning, is thought to induce an endogenous protective environment, consisting of humoral and neuronal-mediated responses that promote cell survival/repair and dampen apoptotic/inflammatory pathways, mitigating ischaemic injury.[11] These protective mechanisms do not seem organ-specific, exerting systemic and remote protective effects; thus, remote ischaemic pre-conditioning (RIC) applied to a limb can promote tolerance to cerebral ischaemia.[10] The RIC stimulus appears to precipitate not only an early phase of short-term metabolic, energy utilization, and blood-flow changes lasting a few hours, but also a late phase of longer-lasting changes in gene expression, inflammatory, and oxidative pathways (16-96 hours post-RIC).[12] The exact mechanisms for signal transmission from the periphery to the brain to protect against ischaemia remain unclear, so there is uncertainty regarding the optimal

biomarkers of RIC. Candidate biomarkers include circulating nitrite, heat shock protein 27 (HSP-27), microRNA-144, and interleukin-10.[13-16]

In a bilateral carotid occlusion model of VCI in mice, chronic daily RIC demonstrated increased angiogenesis (capillary density), cerebral flood flow, and preservation of white matter myelination at 1-month and 4-months.[17] In humans, RIC has been trialled for percutaneous coronary intervention (PCI) in the setting of acute myocardial infarction,[18 19] elective PCI,[19] and cardiac surgery.[20] RIC has also been studied in the past few years in cerebrovascular disease, mostly applied to the upper-limb but some in the lower-limb,[21-26] and in several studies of peri-/post-conditioning (happening after ischaemic/haemorrhagic injury).[27-29] Bilateral upper-limb RIC protects against recurrent stroke in intracranial arterial stenosis.[22] A systematic review of RIC included three trials (371 participants) for ischaemic stroke prevention and four trials (364 participants) for ischaemic stroke treatment, and found low-quality evidence that RIC reduces recurrent stroke risk in patients with intracerebral artery stenosis and reduces stroke severity in patients undergoing carotid stenting.[30] There is also preliminary evidence of efficacy for this therapy in cSVD. A trial of 17 patients with cSVD randomised to RIC or sham-RIC reported improved mean flow velocity of the middle cerebral artery, lower dizziness handicap inventory score, and lower post-treatment WMH volume in the RIC group.[23] A trial in 36 patients with cSVD reported a significant reduction in WMH volume at 1-year compared to sham-RIC and a significant difference on visuospatial and executive function sections of the Montreal Cognitive Assessment (MoCA), though there was no significant change in the number of lacunes.[24]

Prior studies of RIC in cSVD have been small and essentially hypothesis-generating, and several uncertainties remain. First, the required “dose” of RIC sessions to observe a favourable effect is uncertain: a number of published studies have used bilateral upper-arm RIC twice daily,[22 24] but if similar results are obtained with once-daily and/or single upper-arm sessions,

this would be especially appealing for patients and facilitate treatment adoption. Importantly, human[31] and animal model[32 33] studies show that single limb RIC with only 3-4 cycles can reduce end organ ischaemic damage. The most comprehensive dose-finding study[33] found that more than one limb, more than four cycles, and more than 5-minutes of ischaemia conferred no additional reductions in infarct size in a mouse model of acute myocardial infarction. Second, most of the published studies have reported an exceptionally high rate of patient compliance (>80%), even with bilateral upper-arm, twice-daily sessions – requiring at least 100 minutes daily, during which they can do little meaningful activity. It is uncertain whether similarly high rates of compliance can be expected in the trial target population of persons with objective evidence of cognitive impairment. Third, the persistence of treatment effects beyond the cessation of RIC – as suggested by the "late phase" of RIC-related physiological changes suggested by laboratory studies[17] – remains to be demonstrated. The aforementioned mouse model of bilateral carotid occlusion showed similar efficacy of RIC in mice receiving 1-month or 4-months of therapy,[17] but it is unclear if such persistence can be seen in humans. Fifth, prior cSVD trials (including of non-RIC treatments) have suffered from common methodological problems including a lack of neuroimaging for diagnosis and classification, low quality trial design (lack of intent-to-treat analysis or pre-specified primary outcomes, failure to account for multiple comparisons), and lack of use of biomarkers for monitoring and treatment response.[34]

Therefore, we propose an early phase trial to lay the foundation for a research program to further investigate the effect of RIC on prevention of cognitive decline caused by brain infarction from cSVD. We will examine whether different doses of daily RIC performed for 1-month are tolerable and safe, whether they result in improved cerebral blood flow, and whether the biomarker effects of 1-month of treatment are sustained at 3-months.

## METHODS AND ANALYSIS

### Study design

TRIC-VCI will be a prospective, open-label RCT with blinded endpoint assessment (PROBE)[35] and a run-in period, testing two regimens of remote ischaemic preconditioning. The trial scheme is shown in **Figure 1**. The trial is registered at clinicaltrials.gov (NCT04109963). This manuscript described protocol version 2.0.

The trial will begin with a "run-in" period of 14-days in which all patients will be asked to perform once-daily single-arm RIC. Participants that demonstrate >80% completion of treatment sessions (i.e. at least 12 of 14 sessions based on review of device records) will then be randomised to either: (1) RIC performed once a day on one arm, or (2) RIC performed twice a day on one arm.

### Intervention

Each RIC session will consist of 4 cycles of unilateral upper arm ischaemia for 5-minutes followed by reperfusion for another 5-minutes. The procedure will be performed by using an electric auto-control device (manufactured by Seagull Apps, Denmark) with cuffs that inflate to a pressure of 200 mmHg during the ischaemic period (**Figure 2**). This will first be demonstrated by a clinic-based nurse and will subsequently be performed by the patient at home, once or twice daily according to the randomised treatment assignment. The device records and documents each RIC cycle. The RIC process can be stopped at any time by the subject, if the subject experiences any major discomfort.

Patients will be required to tolerate the treatment and demonstrate >80% completion of treatment sessions (i.e. at least 12 of 14 sessions) to proceed to randomisation. The device will document each RIC cycle. Recordings will be obtained from the device at the in-person

randomisation visit (to determine whether the participant is eligible to be randomised based on adherence during the run-in period) and 30-day visits. The proportion that complete the run-in period will be a secondary endpoint.

**Discontinuation from study treatment**

If any of the following criteria are met at any time, treatment will be discontinued:

1. Patient declares unwillingness to proceed with the intervention.
2. Treatment is interrupted for >48 hours for any reason.
3. Diagnosis of deep venous thrombosis (DVT) or pulmonary embolism.
4. Surgery on the upper extremity is performed or clinically indicated prior to cessation of the 30-day active treatment period.
5. Initiation of anticoagulation is clinically indicated.
6. Patient develops any other serious adverse event deemed by the attending physician to merit cessation of RIC.

The time-point of discontinuation will be recorded as accurately as possible (using the device data) to determine the total number of actual treatment days for each patient. All patients will be followed to the end of the study period and analyzed in their assigned treatment arm.

**Randomisation scheme**

All subjects will be enrolled in this study consecutively and randomised into the two treatment groups in a 1:1 ratio. Randomisation will be conducted using a web-based algorithm with treatment assignment allocated by web-based real-time interaction with the site. Treatment assignments will be made using the Permuted Blocks method with randomly selected block sizes of 2, 4, or 6.

**Methods for protecting against bias (blinding)**

Participant assignments will not be concealed from the treating physicians or subjects. Investigators and outcome assessors responsible for evaluating the results of cognitive testing, activities of daily living, neuroimaging, and plasma testing will be blinded to the treatment assignment. After enrolment of each subject the site will designate a blinded evaluator (declared in the randomisation form) to perform the 30-day and 90-day follow-up evaluations. This individual cannot be involved in the care of the subject and must remain blinded to treatment assignment of the subject. Patients will be instructed not to disclose their treatment group to the evaluator. All neuroimaging end-points will be determined by the core imaging laboratory blinded to treatment allocation.

**Inclusion and exclusion criteria**

Full details of the inclusion and exclusion criteria are listed in **Table 1**. Briefly, we will enrol patients with mild vascular neurocognitive disorder, or the earlier stages of major vascular neurocognitive disorder. This will include patients with neuroimaging evidence of a significant burden of cerebral small vessel disease, objective evidence of cognitive impairment (MoCA ≤24) but independent in basic ADLs, and for whom concerns regarding cognition are expressed by the patient, caregiver, or referring clinician. To target patients in the milder range of cognitive impairment we will exclude patients with MoCA <13.

Participants with small cortical infarcts will be allowed but patients with larger (>10mm axial diameter) cortical infarcts will be excluded. This is because large destructive lesions may confound study assessments of the impact of progressive cSVD by independently causing clinical disabilities (aphasia, anosognosia, etc) or by confounding neuroimaging processing pipelines. For similar reasons, we exclude patients with a prior history of stroke-related disability, who by definition will not meet our inclusion criterion of being independent for basic activities of daily living.

**Frequency and duration of follow-up**

After their initial recruitment into the study (screening visit), all patients will receive instruction on how to use the RIC device. They will be asked to perform RIC therapy once daily, in one arm, for a total of ≥14 days ("run-in" period). This will be followed by a telephone follow-up visit intended to assess and address tolerability and compliance issues at 1- to 3-days after beginning the run-in period, and to provide further education on how to use the device. Another in-person clinic visit may be scheduled, at the discretion of the site investigator, if further training and education are needed.

Patients will be required to tolerate the treatment and demonstrate >80% completion of treatment sessions (i.e. at least 12 of 14 sessions) to proceed to randomisation. At the randomisation visit (occurring as soon as possible, but not sooner, than 14-days into the run-in period), patients who meet adherence targets will be randomly allocated to one of the 2 treatment groups. A telephone follow-up visit will be done 1-3 days after randomisation, to assess and address tolerability and compliance issues. A similar telephone visit will be performed at 15±3-days to further encourage compliance.

Patients will stop their assigned treatments on day 30±3 days post-randomisation, at which point they have an in-person follow-up visit. A final follow-up in-person visit will occur at 90±3 days post-randomisation (approximately 2 months free of RIC).

Near study close out, participants and their care partners at the Calgary study site will be invited to participate in an exit interview in a group setting regarding their experiences in the trial. We will aim to include 4-6 participants with their care partners.

**Primary and secondary outcome measures**

The primary feasibility/compliance outcomes will be adherence rate at 30 days, defined as the percentage of sessions completed (number of sessions completed / [number of sessions per day x number of scheduled days of therapy]).

Secondary safety/tolerability and efficacy endpoints are specified in **Table 2.** The main efficacy endpoints include change in cognitive test scores on the MoCA,[36] Trail-Making A and B,[37] Controlled Oral Word Association,[38 39] and CERAD 10-item word list learning[40] at 30-days and 90-days, change in MRI peak skeletonized mean diffusivity of the white matter,[41] and change in white matter hyperintensity volume.

The specifications of how these outcome measures will be measured are presented in **Supplementary File 1.**

**Procedures and variables**

The schedule of procedures and variable collection for the trial is presented in **Table 3**. Details of study assessments at each visit are presented in **Supplementary File 2**. Cognitive testing and MRI will be done at randomization, 30 days, and 90 days.

**Sample size justification**

The selected sample size is based on the precision for measurement of the primary outcome (adherence rate), feasibility based on recruitment rate and funding, and the desire to avoid exposing an unnecessarily large number of trial participants to an intolerable treatment arm. With 12 subjects per study arm, if 83% adhere to the treatment arm (meeting our pre-specified outcome of ≥80% adherence) then we can predict with 95% confidence that the true adherence

rate is 52% to 98%. This would provide enough confidence to proceed to a subsequent phase 2 study with a randomised sham control.

Sample size calculations for biomarker efficacy are based on the ability to restore more normal gray matter CBF in patients with VCI due to cSVD. Prior literature on CBF measurements in cSVD has recently been systematically reviewed[42]. Based on a prior study of cSVD VCI patients,[43] we estimate gray matter CBF will be 37.8±12.4 mL/100g brain tissue/minute in cSVD and 55.8±12.4 mL/100g/minute in age matched healthy controls. We estimate that RIC will restore 52% of normal CBF (i.e. an increase to 46.8 mL/100g/minute), as seen in an animal model of VCI[17]. CBF can be measured with good precision using MRI PCASL (estimated within-subject coefficient of variation 4.1% based on two studies[44 45]). Based on these assumptions and two-tailed alpha=0.05, the current trial will provide >99% power to detect a mean increase of 9 mL/100g/min CBF from baseline within each arm. For a future phase 2b study, a sample size of 32 in each arm would provide 80% power and a sample size of 42 in each arm would provide 90% power to determine whether RIC increases CBF by 9 mL/100g/minute compared to a sham control.

**Recruitment strategy and projected recruitment rate**

Patients will be screened at specialty Stroke/TIA clinics and Cognitive clinics (generally staffed by neurologists, geriatricians, or psychiatrists) at each of the study sites. The initial screening can be done by clinicians as part of usual care, since a number of the evaluations needed to determine study eligibility (clinical history of cognitive symptoms, MoCA, and neuroimaging) are commonly used clinical tests recommended by Canadian clinical guidelines. We aim for a recruitment rate of 1 patient per month per site (5 per month across all sites), aiming to achieve our target sample size of 24 in 7-8 months.

**Number of centers**

There are five participating sites across Canada: University of Calgary (lead site), University of British Columbia, McMaster University, University of Toronto, Western University.

**Proposed Analysis**

Primary and secondary outcomes will be compared between the two study groups (or in all subjects at the end of the run-in phase, as specified), with intent-to-treat analysis. To investigate the sustainability of changes at 90-days (60-days after ceasing RIC) and 30-days for relevant secondary outcomes, tests will compare the two treatment groups at 30-days and then the two treatment groups at 90 days. Given the relatively small sample size, normality assumptions will be based on prior literature and not testing within the trial data set.

The primary outcome, adherence rate at 30-days, will be calculated as: number of sessions completed / [number of sessions per day x number of scheduled days of therapy]). Subjects are expected to complete 27-33 days of therapy, per protocol. Fisher's exact test will be used to compare proportions completing ≥80% of assigned sessions. The mean number of sessions completed will be compared by analysis of variance (ANOVA).

The statistical test for each secondary outcome is specified in **Table 2**.

For the qualitative exit interview with study participants, an audio recording of the group session will be transcribed and analyzed for emerging themes regarding the ease of use of the RIC device, the quality of the user manual and other patient instructions, the tolerability of the treatment, and advice for conduct of future trials.

**Handling of missing data**

Baseline characteristics and treatment assignments of patients with and without missing data will be compared to identify any significant differences that might affect the interpretation of results. Given the relatively small sample size, we will not perform multiple imputation on missing data.

**Subgroup analyses**

A priori subgroup analyses will include assessing tolerability and treatment effects by age, sex, self-reported physical activity level, and baseline burden of SVD.

**Patient and public involvement**

Patients and the public were not directly involved in the design of the study. However, the primary and secondary outcomes are focused on assessing the burden and tolerability of the intervention for patients, in preparation for larger scale trials. As noted above, we will also be conducting a qualitative interview near study close-out to obtain feedback from the patients based on their experience, thereby giving them a voice in subsequent trial designs. Study results will be disseminated through patients and study participants through our institution's social media platform and the website of the Canadian Consortium on Neurodegeneration (www.ccna-ccnv.ca).

## ETHICS AND DISSEMINATION

### Ethical Considerations

This protocol and the informed consent document have been reviewed and approved by the Conjoint Health Research Ethics Board at the University of Calgary. A signed consent form must be obtained from the subject at the screening visit prior to the "run-in" period or any other study procedures (**Supplementary File 3**). The consent form describes the purpose of the study, the procedures to be followed, and the risks and benefits of participation. Consent will be obtained by a physician investigator or coinvestigator. Ethics approval, including for protocol and consent changes, is required by separate review boards at each study site. Declarations of competing interests are provided to the ethics boards and will be included with manuscript submissions.

### Data management

De-identified data will be housed and managed in a password-protected custom database at the University of Calgary Clinical Research Unit. The data will be supported by an FDA compliant commercial database (iDATAFAX) which will allow electronic data capture (EDC) or fax-back data capture on a site-by-site basis. Sites will maintain patient identifiable source data in a secure location. The trial principal investigator and co-investigators will have access to the data.

### Data recording

The Sponsor-Investigator (and any Participating Site Investigators) will maintain adequate and accurate records to enable the conduct of the study to be fully documented and the study data to be subsequently verified. These documents are classified into two different separate categories: (1) Investigator's Study File; and (2) subject clinical source documents.

The Investigator's Study File will contain the protocol/amendments, Case Report and Query Forms, IEC/IRB/governmental approval with correspondence, all versions of ethics approved informed consent forms, staff curriculum vitae and authorization forms and other appropriate documents/correspondence.

Subject clinical source documents would include subject hospital/clinic records, physician's and nurse's notes, appointment book, original laboratory reports, imaging reports, completed case report forms (CRFs) (Supplementary File 4), any relevant pathology and special assessment reports, signed ICFs, consultant letters, and subject screening and enrolment logs.

For each subject enrolled, a CRF will be completed and signed by the Sponsor-Investigator (and any Participating Site Investigator) or authorized delegate from the study staff. This also applies to records for those patients who fail to complete the study (even during a pre--randomisation screening period if a CRF was initiated). If a subject withdraws from the study, the reason must be noted on a CRF. If a subject is withdrawn from the study because of a treatment-limiting AE, thorough efforts will be made to clearly document the outcome.

**Monitoring**

All data will be monitored centrally by the coordinating center at the University of Calgary for accuracy and completeness. The initial performance-monitoring assessment will take place after the initial subject is enrolled, and the next monitoring assessment will take place at close out. The close-out monitoring assessment will take place at the completion of subject enrolment and protocol required follow-up visits at the performance site. Monitoring visits will be done remotely by teleconference, but the coordinating center reserves the right to conduct on site monitoring at its discretion. The monitor will verify the adequacy of site facilities and staff, site recruitment, subject randomisation, documentation of informed consent, and the presence of regulatory

documents. During the monitoring visit, any omissions/corrections to data submitted to the database are noted and queries are generated by the monitor. At close out, sites are instructed in the record retention of all trial documents. Principal Investigators will issue a final report to the ethics board.

Details on study coordination, the steering committee, data processing, audit and inspection, and archiving protocols are presented in **Supplementary File 5.**

**Safety and Adverse Events**

Adverse events should be reported as they occur on the CRF. Documentation must be supported by an entry in the subject's file. Each event should be described in detail along with start and stop dates, severity, relationship to the therapy as judged by the Investigator, action taken and outcome. Serious adverse events (SAEs) must be reported within 1 business day of the local investigator or outcome assessor's first awareness of its occurrence. SAEs will be reviewed by the trial medical monitor. Because this is not a regulatory trial, SAEs do not require reporting to Health Canada or other regulatory authorities. Because the adverse event profile of RIC has been quite benign in previous trials, we do not predict that there will be unexpected SAEs.

Safety outcomes of DVT and PE, arm neurovascular injury, and serious adverse events will be adjudicated by a medical monitor, an independent neurologist with experience in clinical trials, who will report these events to the Steering Committee.

**Data dissemination**

Results will be disseminated through peer-reviewed publications, professional organisations, and conferences. The de-identified study dataset and analysis code will be posted to the

University of Calgary section of the PRISM dataverse at the time of publication of the main study results.

The data from this trial will be used to inform decisions on study design for a subsequent phase 2b trial including: 1) the frequency and intensity (one limb or two limbs) of RIC, based on adherence and safety data, 2) the choice of clinical cognitive and functional tests and assessment scales, based on feasibility and reliability, and 3) the choice of biomarkers, based on feasibility, reliability, and sensitivity to change over time.

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## AUTHOR STATEMENT

AG assisted with the design of the study protocol, drafted the first version of the manuscript, and prepared subsequent revisions. PAB, DC, SEB, TSF, RF, VCH, ZI, LMM, CRM, DJS, MS, and RHS participated in the revisions of the study protocol, read and reviewed the manuscript, and approved the final version of the manuscript. EES conceived, designed, and supervised the study protocol, read and reviewed the manuscript, and approved the final version of the manuscript.

## DATA AVAILABILITY

The de-identified study dataset and analysis code will be posted to the University of Calgary section of the PRISM dataverse at the time of publication of the main study results.

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## CONFLICTS OF INTEREST

Dr. Ganesh has a patent pending for a system to deliver remote ischemic conditioning, not related to the device (or manufacturer) being used in this trial. Dr. Smith reports consulting fees from Alnylam Pharmaceuticals and Biogen; and royalties from UpToDate.

## TABLES

**Table 1. Inclusion and Exclusion Criteria for the TRIC-VCI study**

| Inclusion Criteria | Operationalized as: |
|---|---|
| 1. Evidence of cerebral small vessel disease on CT or MRI | Evidence of either:<br>1. Beginning confluent WMH (ARWMC[46] grade 2) on any slice on CT or MRI<br>OR<br>2. Two or more supratentorial subcortical infarcts |
| 2. Objective evidence of cognitive impairment | MoCA[36] score ≤24 |
| 3. Concern on the part of the patient, caregiver, or clinician that there has been a decline from previous level of cognitive functioning | AD8 questionnaire[47] (administered to informant) with 2 or more positive responses, or clinical judgement based on self report of participant or observations by examiner |
| 4. Independent with basic daily activities of living | BADLS[48] response (a) for questions 2, 4, 5, 6, 7, 8, 9, and 14. |
| 5. Age 60-85 | |
| **Exclusion Criteria** | |
| 1. Cortical infarcts larger than 10 mm axial diameter. | Based on site review of clinical CT or MRI |
| 2. Symptomatic ischemic or hemorrhagic stroke occurring within the last 90 days | |
| 3. Neuroimaging evidence of mass lesion, intracerebral haemorrhage, vascular malformation, or evidence of non-vascular disease such as hydrocephalus. | Based on site review of clinical CT or MRI. Microbleeds are allowed. |
| 4. Residence in long-term care facility. | |
| 5. Other significant neurological or psychiatric disease (e.g. multiple sclerosis). | |
| 6. Subject does not have a study partner who can provide corroborative information. | Partner is required to complete the BADLS and MBI-Checklist.[49] |
| 7. English or French is not sufficiently proficient for clinical assessment and neuropsychological testing. | |
| 8. Total score on the MoCA <13 | |
| 9. Unable to undergo MRI due to medical contraindications or inability to tolerate the procedure. | |
| 10. Co-morbid medical illness that in the judgment of the study investigator makes it unlikely that the participant will be able to complete three months of study follow-up. | |

| | |
|---|---|
| 11. On therapeutic anticoagulation with doses used for treatment of deep venous thrombosis, pulmonary embolism, or for stroke prevention in atrial fibrillation. | Lower dose anticoagulation for prevention of coronary artery disease, e.g. rivaroxaban 2.5 mg po bid, will be allowed. |
| 12. Significant bleeding diathesis. | Including but not limited to hemostatic disorder, platelet count <100 x $10^9$/L, INR >1.7, history of liver cirrhosis. |
| 13. Any symptomatic or previously known arm soft-tissue disease, vascular injury, or peripheral vascular disease. | Defined as patients with symptoms of vascular claudication or prior arterial thromboembolism in limbs. |
| 14. Hypertension with systolic blood pressure ≥180 mmHg despite medical treatment at the time of enrolment. | |
| 15. Planned revascularization (any angioplasty or vascular surgery) within the next three months. | |
| 16. Planned surgical procedure within the next three months. | |
| 17. Currently receiving an investigational drug or device by other studies | |

**Table 1 Legend:** ARWMC, Age-related White Matter Changes; BADLS, Bristol Activities of Daily Living Scale; CT, computed tomography; MBI checklist, mild behavioural impairment checklist; MoCA, Montreal Cognitive Assessment; MRI, magnetic resonance imaging.

**Table 2. Secondary endpoints for the trial and the statistical test to be used for each**

| Secondary safety/tolerability endpoints | Statistical test of choice |
|---|---|
| 1. Discontinuation prior to 30-days | Fisher's exact test |
| 2. Proportion completing the run-in period and entering the randomisation phase | Fisher's exact test |
| 3. Physical examination signs of tissue or neurovascular injury resulting from RIC treatment at 30-days | Fisher's exact test |
| 4. Development of symptomatic upper extremity deep vein thrombosis at 30-days and 90-days | Fisher's exact test |
| 5. Peak and end-cycle pain levels reported by the participant using the Visual Analog Scale during the 30-day treatment period | Repeated measures analysis with linear mixed models will be used to estimate the mean VAS per session, using all VAS data and including the subject as a random effects term to account for within-subject correlation. Peak and end VAS will be analyzed in separate models. The proportion with intolerable pain, defined as estimated mean VAS >8, will be compared by Fisher's exact test. Subjects with insufficient VAS data, defined as <3 recorded VAS peak or <3 recorded VAS end levels, will be excluded from these analyses |
| Secondary efficacy endpoints | |
| 1. Change in MRI WMH volume at 30-days and 90-days | Volumes at baseline and follow up will be logarithmically transformed (natural log) to give a more normal distribution. Then differences between each group will be compared using a linear mixed model |
| 2. Change in MRI diffusion tensor imaging (DTI) peak skeletonized mean diffusivity[41] (PSMD) at 30-days and 90-days | Linear mixed model, testing difference at 30-days and 90-days. |
| 3. Number of new MRI infarcts at 30-days and 90-days | Fisher's exact test |
| 4. Number of new MRI DWI-positive lesions at 30-days and 90-days | Fisher's exact test |
| 5. Change in MRI ASL gray matter cerebral blood flow at 30-days and 90-days | Linear mixed model, testing difference at 30-days and 90-days. |
| 6. Change in MoCA[36] score at 30-days and 90-days | Linear mixed model, testing difference at 30-days and 90-days |
| 7. Change in Trail-Making A and B[37] at 30-days and 90-days | Volumes at baseline and follow up will be logarithmically transformed (natural log) to give a more normal distribution. Linear mixed model, testing difference at 30-days and 90-days |

| | |
|---|---|
| 8. Change in Controlled Oral Word Association[38 39] score at 30-days and 90-days | Linear mixed model, testing difference at 30-days and 90-days. |
| 9. Change in CERAD 10-item word list learning[40] score at 30-days and 90-days | Linear mixed model, testing difference at 30-days and 90-days |
| 10. Change in total score on MBI Tracking Tool, adapted from the MBI Checklist[50], at 30-days and 90-days | Linear mixed model, testing difference at 30-days and 90-days |
| 11. Change in BADLS[48] at 30--days and 90-days | Linear mixed model, testing difference at 30-days and 90-days |
| 12. Difference in candidate blood biomarkers at 30-days and 90-days | Linear mixed model, testing difference at 30-days and 90-days |

**Table 3. Overview of the schedule of procedures and variable collection**

| | Visit | | | | | |
|---|---|---|---|---|---|---|
| | **Screening** | **Random-ization** | **Phone Fu** | **Phone Fu** | **F/u** | **End** |
| **Activity** | 0 | Within 30 d | 1-3 d | 15±3 | 30±3 | 90±3 |
| Written consent | ✓ | | | | | |
| Demographics | ✓ | | | | | |
| Medical history | ✓ | ✓ | | | ✓ | ✓ |
| Medications | ✓ | ✓ | | | ✓ | ✓ |
| Physical exam | ✓ | ✓ | | | ✓ | |
| NIH Stroke Scale | ✓ | ✓ | | | ✓ | ✓ |
| Hachinski ischaemic score | ✓ | | | | | |
| MoCA | ✓ | ✓ | | | ✓ | ✓ |
| Bristol Activities of Daily Living Scale | ✓ | ✓ | | | ✓ | ✓ |
| AD8 Informant Questionnaire | ✓ | | | | | |
| IQCODE | ✓ | | | | | |
| Inclusion/exclusion criteria | ✓ | | | | | |
| RIC device provision | ✓ | | | | | |
| RIC device training | ✓ | ✓ | ✓ | ✓ | | |
| Subject diary provision | ✓ | | | | | |
| Subject diary review | | ✓ | | | ✓ | |
| Adherence (device print out) | | ✓ | | | ✓ | |
| Randomisation | | ✓ | | | | |
| Cognitive tests | | ✓ | | | ✓ | ✓ |
| MBI Checklist | | ✓ | | | ✓ | ✓ |
| Blood draw | ✓ | ✓ | | | ✓ | ✓ |
| MRI | | ✓ | | | ✓ | ✓ |

**FIGURES**

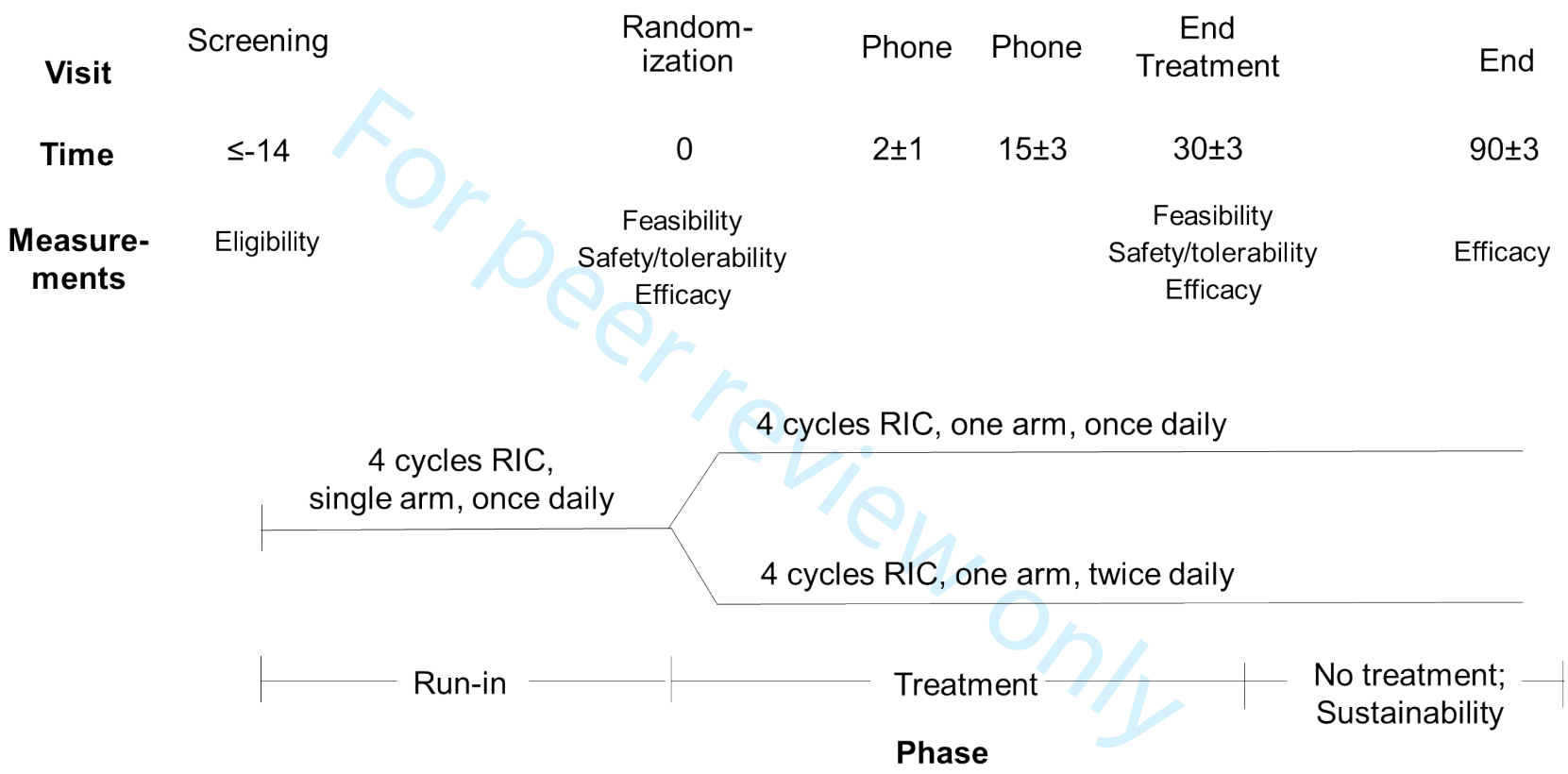


**Figure 1.** Trial design for the TRIC-VCI study.

**Figure 2.** Device for applying remote ischemic conditioning (Seagull Aps, Denmark). The device applies four cycles of remote ischemic conditioning upon pressing the button. Device activations are recording, including the number of cycles. Systolic blood pressure, diastolic blood pressure, and pulse are displayed.

| Visit | Screening | Randomisation | Phone | Phone | End Treatment | End |
|---|---|---|---|---|---|---|
| **Time** | ≤-14 | 0 | 2±1 | 15±3 | 30±3 | 90±3 |
| **Measure-ments** | Eligibility | Feasibility<br>Safety/tolerability<br>Efficacy | | | Feasibility<br>Safety/tolerability<br>Efficacy | Efficacy |

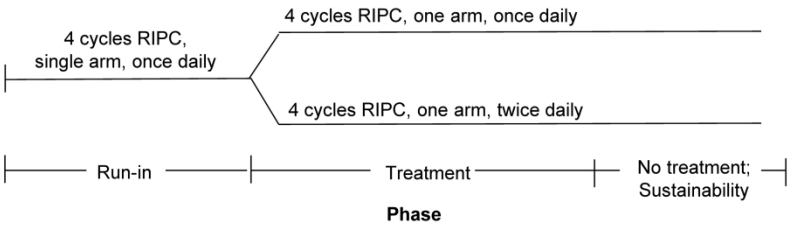


Figure 1. Trial design for the TRIC-VCI study.

159x76mm (600 x 600 DPI)


Figure 2. Device for applying remote ischemic conditioning (Seagull Aps, Denmark). The device applies four cycles of remote ischemic conditioning upon pressing the button. Device activations are recording, including the number of cycles. Systolic blood pressure, diastolic blood pressure, and pulse are displayed.

101x64mm (300 x 300 DPI)

**SUPPLEMENTARY FILE 1: HOW OUTCOME MEASURES WILL BE MEASURED**

| **Outcome Measure** | **Measurement or operationalized definition** |
|---|---|
| **Feasibility Outcomes** | **All measured at the point of randomization as well as at 1-month (including only randomized patients)** |
| Adherence – the number of sessions completed (maximum 30±2); good adherence defined as ≥80% completion | Determined by automated real-time recording of the RIC device. Study staff will print out the recording from the device at the time of follow-up. defined as the percentage of sessions completed (number of sessions completed / [number of sessions per day x number of scheduled days of therapy]. If the patient discontinues therapy prior to the 30 days, the denominator scheduled days of therapy will be defined as 30. |
| Discontinuation rate | Defined as:<br>1. Patient declares unwillingness to proceed with the intervention, OR<br>2. Patient develops serious adverse event deemed by attending physician to merit cessation of RIC. |
| **Safety and Tolerability Outcomes** | **All measured at the point of randomization as well as at 1-month (including only randomized patients)** |
| Any serious adverse event deemed by attending physician to merit cessation of RIC. | Will include arm tissue or neurovascular injury or upper extremity deep venous thrombosis. |
| Objective signs of tissue or neurovascular injury resulting from RIC treatment | Inspection by observers blinded to the study protocol which will include palpation of distal radial pulses, visual inspection for local edema, erythema, skin breakdown and/or other skin lesions, and palpation for tenderness. |
| Development of symptomatic upper extremity deep vein thrombosis | As demonstrated on extremity ultrasound, to be obtained only if clinically indicated by the attending physician based on follow-up examination of the upper limb. |
| Pain or discomfort | Rated on follow-up assessments using the Numeric Rating System NRS which requires participants to self-report an |

| | |
|---|---|
| | integer ranging from 0 (no pain) to 10 (worst imaginable pain).[45] To help participants choose the appropriate pain level, the Wong Baker FACES Pain scale[46] will be displayed along with the NRS. The Wong Baker scale has been validated in persons with cognitive impairment[47]. "Intolerable pain" will be defined as intra-subject mean NRS>8, corresponding with "hurts a whole lot" on the Wong Baker FACES Pain scale. |
| **Efficacy Outcomes** | **All measured at 1-month and 3-months** |
| Change in cerebral blood flow | Change in cerebral gray matter blood flow on arterial spin-label (ASL) MRI. |
| Change in MRI WMH volume | MRI FLAIR images will be processed for WMH volume using semi-automated Quantomo software (Cybertrials, Inc) at the University of Calgary Stroke Core Imaging Lab. A single blinded rater qualified by the Stroke Core Imaging Lab will measured WMH volume on the three scans from each trial subject, blinded to scan order. |
| Change in MRI DTI PSMD | A single assessor from the Stroke Core Imaging Lab will determine PSMD[42] on each scan, using the processing pipeline described at http://www.psmd-marker.com/, blinded to treatment status. |
| New brain infarct | A single neurologist or neuroradiologist qualified by the Stroke Core Imaging Lab will review each scan for chronic infarcts and new infarcts. Recent small subcortical infarcts and lacunar infarcts will be defined according to Standards for Reporting Vascular Changes on Neuroimaging (STRIVE)[2]. Cortical infarcts will be defined as areas of focal enchephalomalacia with T1 hypointensity and T2 hyperintensity in the distribution of a vascular territory. Small (<5 mm) cortical infarcts will be defined according to recent consensus criteria for "microinfarcts"[48]. |
| New DWI positive lesion | A single neurologist or neuroradiologist qualified by the Stroke Core Imaging Lab will review each scan for DWI |

| | |
|---|---|
| | positive lesions. Apparent Diffusion Coefficient (ADC) maps will be reviewed to exclude confounding T2 shine through from chronic lesions, but ADC hypointensity is not required to be present. Small DWI positive lesions (< 5 mm) will be defined according to recent consensus criteria for acute "microinfarcts"[48]. |
| Cognitive decline | Change in scores from pre- to post-treatment:<br>1. Mean change in total MoCA scores.<br>2. Proportion with decline in total MoCA ≥2 points.<br>3. Mean change in MoCA visuospatial/executive subscore.<br>4. Mean change in Trail-Making Test A and B scores. |
| Functional decline | Change in BADLS total score[41]. |
| Change in neuropsychiatric symptoms | Change in total score on the MBI Tracking Tool, adapted from the MBI Checklist[44]. |
| Candidate Biomarkers | All measured in venous blood:<br>1. Homocysteine<br>2. Circulating nitrite<br>3. Interleukin-10<br>4. Matrix metalloproteinase 2 and 9<br>5. TNF-alpha<br>6. Interferon gamma<br>7. MicroRNA-144<br>8. SDF-1-alpha<br>9. Heat shock protein 27 |

## SUPPLEMENTARY FILE 2: DETAILS OF STUDY ASSESSMENTS AT EACH VISIT

### Screening visit

At the first screening visit, patients who are deemed by the attending physician to potentially be eligible for the study will sign consent and then undergo a detailed clinical assessment to ensure that they meet inclusion criteria and do not meet any exclusion criteria. Participants who do not meet study selection criteria at the end of the visit will be deemed screen failures, will cease participation in the study, and will not be counted toward the target study sample size.

The screening visit assessment are:

- Demographic characteristics
- Medical histories, including vascular risk factors, previous history, concomitant medication, and family history
- Information about the participants' general levels of physical activity
- Physical examination including blood pressure assessment, NIH Stroke Scale (NIHSS)[49], examination of the arms for any severe soft tissue injury or evidence of ischemia that would be deemed a RIC contraindication.
- Hachinski Ischemic Score[50].
- Cognitive performance, using the MoCA.
- Informant reports of cognitive decline and functional status using BADLS, AD8, and IQCODE short form[51] questionnaires *(if patient does not attend with an informant, then the informant may be contacted by telephone or post to complete these assessments).* If there is a history of past symptomatic stroke, then the Rankin Focused Assessment will also be administered and used to determine the modified Rankin Scale score.
- Review of neuroimaging (CT or MRI) obtained clinically within the last year, to document neuroimaging eligibility criteria. CT or MRI are recommended by clinical consensus criteria and medical guidelines for diagnosis of stroke, cSVD, or neurocognitive disorders[52,53].

All patients meeting inclusion criteria will be invited to participate in the 14-day minimum run-in period. They will be taught how to use the RIC and will be observed performing a full session (4 cycles of ischemia and reperfusion) to ensure that they are using the device correctly, before being sent home with the device.

**Randomization visit**

After the 14-day run-in period, feasibility, safety, and tolerability outcomes will be evaluated for all the recruited patients, as outlined in the table above. Completion of ≥80% of RIC sessions, lack of significant safety concerns by the site investigator, patient willingness to proceed, and verification that the subject continues to meet all study inclusion and exclusion criteria are required to proceed to the next phase of the study including cognitive testing, activities of daily living, and randomization, followed by MRI, blood draw and provision of the patient diary.

Medical history: Intervening clinical stroke, new medical diagnoses, new surgeries, change in medications.

Physical examination: NIH Stroke Scale score, arm examination.

Print out of recorded sessions on device: The RIC device will print out the number of completed sessions. By comparing the number of recorded sessions with the total number of expected sessions, study staff will determine whether ≥80% of the expected sessions have been completed. If <80% of the expected sessions have been completed, the participant will not be randomized and subject participation will cease. If ≥80% of the expected sessions have been completed then the subject will continue with the study visit to verify that all inclusion and exclusion criteria are still met and, if appropriate, to undergo randomization and biomarker testing.

Cognitive testing**:** MoCA, plus a brief neuropsychological test battery. Test choices are based on recommendations for VCI research from the Canadian Stroke Network and National Institute of Neurological Disorders and Stroke.[54] Performed by a blinded neurologist, neuropsychologist, trained cognitive clinic nurse, or trained study staff.

| Domain | Name | Time (min) |
|---|---|---|
| Processing speed | Trail-Making Part A[43] | 3 |
| Executive | Trail Making Part B[43] | 5 |
| | Controlled Oral Word Association[55,56] | 4 |
| Memory | CERAD 10-item word list learning [57] | 6 |

| | | |
|---|---|---|
| | | Total 18-20 minutes |

Neuropsychiatric symptoms: Mild Behavioural Impairment Tracking Tool (MBI Tracking Toolchecklist) will be completed by the informant. The MBI Tracking Tool is based on the validated Mild Behavioural Impairment Checklist, but adapted to track changes in neurobehavioural symptoms over a span of days to weeks.

Activities of daily living: BADLS will be completed by the informant.

After the above assessments are completed, subjects who continue to meet all study inclusion and exclusion criteria according to the data collected up to this stage are then randomized to either of the two treatment arms. Following randomization, the following study procedures are carried out:

Provision of patient diary including NRS assessments for treatment-related pain and discomfort: The subject will be issued a diary that includes checkbox reminders for their daily at-home RIC sessions, as well as the Numeric Rating Score(NRS) for pain which will be recorded after every session. In the NRS, the subject will be asked to indicate, at the end of the session, with a mark the level of worst pain experienced during the entire session and the level of pain at the end of the last cycle of cuff inflation, ranging from 0 (no pain) to 10 (worst imaginable pain).

Venipuncture for blood draw: Venipuncture will be performed with withdrawal of 20 mL of blood. Blood will be frozen at -80 degrees and shipped to the University of Calgary for analysis in a central laboratory. Blood will be tested for levels of: homocysteine, circulating nitrite, interleukin 10, matrix metalloproteinases 2 and 9, TNF-alpha, interferon gamma, microRNA-144, SDF-1-alpha, and heat shock protein-27. 10 mL of blood will be stored at -80 for potential future use to explore newly emerging biomarkers of RIC response.

MRI scan: Subjects with have an MRI scan that includes the sequences in the following table. MRI sequence parameters are based on the Canadian Dementia Imaging Protocol (https://www.cdip-pcid.ca) and should the match the table below, although slight deviations to account for vendor hardware and software differences are expected to be necessary. MRI field strength will be 1.5T or 3T. MRI quality control will be ensured by: 1) requiring all sites to use a local phantom for MRI quality control according to their own practice, but at minimum adhering

to standards from the American College of Radiology[58], 2) qualification of the site for MRI scanning by review a phantom scan collected at each site, 3) review of each subsequent scan from each site for protocol adherence and quality. Sites are qualified to participate in the study via review and qualification of the phantom scan at each site by the University of Calgary Stroke Core Imaging Laboratory by a core lab-certified radiologist and MR physicist or biomedical engineer. Only sites that demonstrate the ability to acquire protocol-adherent, quality scans are allowed to participate in the trial. The scan quality control processes ensure that study MRI data are collected according to protocol specifications with sufficient quality for analysis of imaging endpoints.

**MRI Sequence Parameters**

| Sequence | TE (ms) | TR (ms) | Voxel size (mm) | Other |
|---|---|---|---|---|
| 3D T1-weighted | min | min | 1x1x1 | TI=650 ms, flip angle=9 |
| Dual echo T2/PD | Min/90 | 3300 | 0.94x0.94x3.0 | Echo train length 12 |
| FLAIR | 120 | 9000 | 0.94x0.94x3.0 | TI 2500 ms, flip angle 90 |
| SWI | 3.3 | 30 | 1x1x2 | flip angle 20 |
| DTI | min | 6000 | 2x2x2 | *b*=1000, 32 directions |
| ASL | | | 2x2x2 | PCASL |

Parameters shown are for a GE 3.0T scanner. Full parameters for all major vendors at 1.5 and 3T will be provided to sites in an MRI procedures manual. Estimated total acquisition time is 32 minutes. TE, echo time; TR, repetition time; TI, inversion time; T2, T2 relaxation time weighted; T1, T1 relaxation time weighted; FLAIR, fluid attenuated inversion recovery; DTI, diffusion tensor imaging; ASL, arterial spin label; PCASL, pseudo-continuous ASL.

**Day 1-3 telephone follow-up visit**

Within three days of randomization (days 1-3) and following at least one RIC session at home by the subject, the patient will receive a telephone call from a research nurse to discuss and potentially trouble-shoot issues with compliance or safety/tolerability.

**Day 15 telephone follow-up visit**

The day 15 telephone visit should be booked within ±2 days. The patient will receive a telephone call from a research nurse to discuss and potentially trouble-shoot issues with compliance or safety/tolerability.

**Day 30 in-person follow-up visit**

The day 30 visit should be booked within ±2 days. Patients will be instructed to use the RIC device up to the day prior to their 30-day follow-up visit. They will undergo the following assessments, all of which will be conducted and interpreted by assessors blinded to the patient's randomization:

- Medical history: Intervening clinical stroke, new medical diagnoses, new surgeries, change in medications.
- Physical examination: NIH Stroke Scale score, arm examination. Done by a blinded assessor.
- Retrieval of patient diary with VAS pain scores
- Cognitive testing: MoCA, Trails A and B, Controlled Oral Word Association, 10-item word list recall, performed by a blinded neurologist/neuropsychologist/trained cognitive clinic nurse.
- Neuropsychiatric symptoms: Mild Behavioural Impairment Tracking Tool will be completed by the informant.
- Activities of daily living: BADLS completed by the informant.
- Venous blood-draw: Blood will be obtained by venipuncture using the same protocol as for the randomization visit, frozen at -80 degrees and shipped to the University of Calgary for analysis in a central laboratory.
- MRI**:** The same protocol will be used as at the randomization visit.

**90-day in-person follow-up visit**

The day 90 visit should be booked within ±2 days. At this visit the following assessments will be done, all of which will be conducted and interpreted by assessors blinded to the patient's randomization:

- Cognitive testing: MoCA, Trails A and B, Controlled Oral Word Association, 10-item word list recall, performed by a blinded neurologist/neuropsychologist/trained cognitive clinic nurse.
- Neuropsychiatric symptoms: Mild Behavioural Impairment Tracking Tool will be completed by the informant.
- BADLS completed by the informant.

- Venous blood-draw: Blood will be obtained by venipuncture using the same protocol as for the randomization visit, frozen at -80 degrees and shipped to the University of Calgary for analysis in a central laboratory.
- MRI**:** The same protocol will be used as at the randomization visit.

**Exit Interview**

Near study close out, participants and their care partners at the Calgary study site will be invited to participate in an exit interview in a group setting regarding their experiences in the trial. We will aim to include 4-6 participants with their care partners. Research staff will lead a qualitative, semi-structured interview designed to elicit information on the participant's experiences within the trial including the ease of use of the RIC device, the quality of the user manual and other patient instructions, the tolerability of the treatment, and advice for conduct of future trials.

UNIVERSITY OF CALGARY

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# CONSENT FORM

**TITLE:** **Trial of Remote Ischemic Pre-Conditioning in Vascular Cognitive Impairment (TRIC-VCI)**

**SPONSOR:** Canadian Institutes of Health Research

**Site Principal Investigator: Dr. Eric Smith**
**403-210-7611**

**Co-Investigators**: Dr. Philip Barber, Dr. Zahinoor Ismail

This consent form, a copy of which has been given to you, is only part of the process of informed consent. It should give you the basic idea of what the research is about and what your participation involves. If you want more details about something mentioned here, or something not addressed, you should feel free to ask. Please take the time to read this carefully and to understand any accompanying information.

## BACKGROUND

You are being asked to consider participating in this study because you have a condition called mild Vascular Cognitive Impairment (also known as vascular mild neurocognitive disorder). In this condition, you or the people close to you have noticed changes in your cognition (memory, processing, or reasoning ability) and there is evidence on a brain scan that it is probably due to little strokes or low brain blood flow.

Remote ischemic conditioning (RIC) is a technique to increase blood flow to the brain. It is intended to be performed daily by patients at home. Each session consists of inflating a blood-pressure cuff around an arm to a pressure sufficient to reduce blood flow to the arm for 5 minutes after which it is kept deflated for 5 minutes to restore normal blood flow. This is repeated four times in each treatment. Inducing this brief period of cut off of blood flow ("ischemia") in an organ (the arm) that is far away ("remote") from the brain, may "condition" the brain to increase blood flow and make the brain less vulnerable to problems like new little strokes.

There are no treatments for mild vascular cognitive impairment that are approved by Health Canada. We are testing different regimens of RIC to see how well this treatment can be implemented by patients. This is the first step in a program intended to see if RIC will be an effective treatment for mild vascular cognitive impairment. Thousands of patients have undergone RIC as part of other research studies, and no major harmful effects have been reported.

## WHAT IS THE PURPOSE OF THE STUDY?

The purpose of this study is to determine whether RIC performed once a day on one arm or twice a day on one arm can be implemented successfully by patients, and whether it will improve cognition, brain imaging and blood markers.

## WHAT WOULD I HAVE TO DO?

You will be asked to attend an **initial screening visit** to assess your eligibility for the trial and receive instruction on how to use the RIC device. You will be asked to attend the visit with a **study partner** – someone who knows you well and may be helping you at home. This person will be asked to complete some forms at the screening visit and each in-person visit thereafter, to gather important information about how you are doing that you may not have noticed yourself. Your study partner will also be asked to provide written consent for their role in this study.

At the screening visit, you will be asked to perform RIC therapy once daily, in one arm, for a total of at least 14 days (**"run-in" period**). This will be followed by a telephone follow-up visit at 1- to 3-days after beginning the run-in period, when you will be asked about any issues or concerns, and to provide further education on how to use the device. Another in-person clinic visit may be scheduled, at the discretion of the site investigator, if further training and education are needed.

The RIC procedure is performed by a blood pressure machine that will inflate the blood pressure cuff to a high pressure, stay at that pressure for 5 minutes, and then deflate. It is normal to have some tingling or discomfort in the arm when the cuff is inflated, but it should go away soon after the cuff deflates. The device records and documents each RIC cycle. You can stop the RIC process at any time if you experience any major discomfort. However, you will be required to tolerate the treatment and demonstrate completion of **at least 12 of 14 treatment sessions** to proceed to the next part of the trial, the randomization visit.

You will be given a **study diary** that includes checkbox reminders for your daily at-home RIC sessions, as well as a scale for pain and discomfort, if you experience any (Visual Analogue Scale). In this scale, you will be asked to mark, at the end of the session, the level of worst discomfort experienced during the entire session and the level of discomfort at the end of the last cycle of cuff inflation, ranging from 0 (no discomfort) to 10 (worst imaginable pain). We expect that most patients will tolerate the RIC sessions.

At the randomization visit, you will be randomly (by chance) placed in one of two groups –

1. RIC once a day on one arm
2. RIC twice a day on one arm

Neither you, the study staff nor the investigator(s) can decide which group you are in. You will have a roughly 50% chance of being placed in either group. You will know which group you are in, but the study clinicians who assess you later to see how things have changed or progressed, will not know which group you are in.

You will be asked to perform RIC as assigned, every day for 30 days. A telephone follow-up visit will be done 1-3 days after randomization, and at 15 days, to help address any issues or concerns with the treatment.

You will stop the assigned treatment on day 30 after randomization, at which point you will be invited to an in-person follow-up visit. A final follow-up in-person visit will occur at 3-months after randomization (2 months free of RIC).

## Procedures

### MRI Scans:

An MRI (magnetic resonance imaging) is an electronic picture of your brain created using a strong magnet instead of x-rays.

Each MRI will take approximately 1 hour to complete. You will lie on your back and enter the MR machine for the study, during which time you will hear loud knocking noises. Other than loud noise, this is a painless and safe procedure. You will be asked to wear hearing protection in the form of earplugs. People with pacemakers, aneurysm clips, cochlear implants, or metal/foreign objects in their eyes are not permitted to undergo MR studies.

There are 3 MRI scans involved in this study – one around the time of the randomization visit, one at 30-days, and one at 90-days.

### Blood Sample Collection:

At the randomization visit and at 30-days and 90-days after randomization, a blood sample (slightly more than 1 tablespoon) will be collected. The blood will be tested in a University of Calgary laboratory for levels of various proteins and nucleic acids that are already thought to be relevant markers of changes in the body with RIC therapy. About half of each blood sample will be stored at -80 degrees Celsius for potential future use to explore new markers of RIC response.

### Cognitive Assessments of Memory and Thinking Skills:

A qualified member of the study staff will administer paper and pencil tests to assess your memory and thinking skills. These assessments will take about 1 hour to complete. Breaks will be allowed if needed.

## HOW MANY PEOPLE WILL TAKE PART IN THIS STUDY?

We plan to include 24 people in this study at approximately five centres within Canada. About 8 people will participate in this study at the University of Calgary. The length of this study for participants is 3.5 months (including the run-in period). The entire study will run for about one year.

## WHAT ARE THE RESPONSIBILITIES OF STUDY PARTICIPANTS?

If you decide to participate in the study, you will be asked to do the following:

- Use the study device in one arm, once daily for 14 days during the “run-in” period.
- Then after the randomization visit, use the study device **as instructed** for 30 days.
- Complete the study diary with Visual Analogue Scale scores for each RIC session.
- Answer questions about your health, your medication history and medications you take
- Complete activities to assess your memory, mood and thinking.
- Have a physical examination at in-person study visits.
- Have your blood taken at the randomization visit, at 30-days, and at 90-days (end of study).

- Have an MRI (magnetic resonance imaging) brain scan done at the randomization visit, at 30-days, and at 90-days after randomization.
- Participate according to the study visit schedule as explained below.

**Screening visit:**
The assessments performed at this visit will determine if you are eligible to participate in the study. The screening visit should take approximately 3 hours to complete. Prior to starting we will review this consent form with you and answer any questions that you may have. If you agree to participate, you will have the following assessments done:

- Review of your health history and medications.
- Physical exam including blood pressure assessment, brief neurological examination, and examination of your arms
- Cognitive assessments and mood assessments. A qualified member of the study staff will administer paper and pencil tests to assess your memory and thinking skills. Breaks will be allowed if needed.
- Your study partner will be asked to complete some questionnaires about your cognition and how you are functioning in your daily life. If your study partner does not attend this appointment, then they will be contacted by telephone or post.
- Any brain CT or MRI scans done within the last year will be reviewed for study eligibility.
- You will be given a study diary that includes checkbox reminders for your daily at-home RIC sessions, as well as a pain scale (Visual Analogue Scale) as described above.

If you meet the criteria for the study, you will be invited to participate in the 14-day minimum run-in period. A blood sample will be collected. You will be taught how to use the RIC and will be observed performing a full session (4 cycles of ischemia-reperfusion) to ensure that you are using the device correctly, before being sent home with the device.

**Telephone follow-up**

You will be contacted by telephone in 1-3 days after the screening visit, when you will be asked about any issues or concerns, and to provide further education on how to use the device. Another in-person clinic visit may be scheduled, at the discretion of the site investigator, if further training and education are needed.

**Randomization visit**

This will happen a minimum of 14 days after the screening visit. It will take about 90 minutes. You will have the following assessment done:

- Review of your health history and medications.
- Physical exam including brief neurological examination and examination of your arms
- Review print-out of recorded sessions on the RIC device
- Review of your study diary
- Cognitive assessments and mood assessments. A qualified member of the study staff will administer paper and pencil tests to assess your memory and thinking skills. Breaks will be allowed if needed.
- Your study partner will be asked to complete some questionnaires about your cognition and how you are functioning in your daily life.

If you complete at least 12 of 14 RIC sessions, are not found to have any safety concerns by the site investigator, are willing to proceed, and continue to meet all study inclusion and exclusion

criteria, you will proceed to the next part of the study and will be randomly (by chance) assigned to one of the three study groups. You will have the following assessments done:

- A blood sample will be collected
- MRI scan of your brain will be performed (this may be a separate appointment)

You will receive further instruction on how to use the device based on your assigned group.

### Day 1-3 telephone follow-up visit

Within three days of randomization and after you have completed at least one RIC session at home, you will receive a telephone call from a research nurse to discuss and potentially trouble-shoot issues or concerns that you may be having.

### Day 15 telephone follow-up visit

Around 15 days after the randomization visit, you will receive a second telephone call from a research nurse to discuss and potentially trouble-shoot issues or concerns that you may be having.

### Day 30 in-person follow-up visit

You will be instructed to use the RIC device up to the day prior to the 30-day follow-up visit (which will be 28-32 days after the previous visit). This visit will take about 90 minutes, plus the time for the brain scan. You will have the following assessments done **by assessors who should not know which group you have been assigned to**:

- Review of your health history and medication changes since the last visit.
- Physical exam including brief neurological examination and examination of your arms.
- Review print-out of recorded sessions on the RIC device, which you will **return** at this point
- Review of your study diary, which you will **return** at this point.
- Cognitive assessments (A qualified member of the study staff will administer paper and pencil tests to assess your memory and thinking skills) and mood assessments. Breaks will be allowed if needed.
- Your study partner will be asked to complete some questionnaires about your cognition and how you are functioning in your daily life.
- A blood sample will be collected.
- MRI scan of your brain will be performed (this may be a separate appointment).

**Please <u>do not</u> tell the assessors which group you have been assigned to, or how many times per day you are using the device.**

### 90-day follow-up visit

At 88-92 days, you will be invited back for a follow-up visit. This will take about 60 minutes. You will have the following assessments done **by assessors who should not know which group you have been assigned to**:

- Cognitive assessments (A qualified member of the study staff will administer paper and pencil tests to assess your memory and thinking skills) and mood assessments. Breaks will be allowed if needed.
- Your study partner will be asked to complete some questionnaires about your cognition and how you are functioning in your daily life.
- A blood sample will be collected

- MRI scan of your brain will be performed (this may be a separate appointment)

**Please do not tell the assessors which group you have been assigned to, and how many times you are using the device.**

## Study end visit

Near the end of the study, after all the participants have been enrolled and completed their visits, we may invite you to participate in a focus group interview with other participants and their spouses or care partners. We will ask you and the other participants questions about your experience with the RIC device. We will give you the opportunity to tell us how we can use the device better in the future. This session may last up to two hours and will be audio-recorded.

**If you need to stop using the RIC device or decide to stop participating in the study**, you will still be invited to come in and complete the assessments scheduled for the 30-day and 90-day visits before leaving the study, if possible.

## WHAT ARE THE RISKS?

You may experience side effects from participating in this study. Some side effects are known and are listed below.

### Study device risks:

Most side effects are mild or moderate and usually transient for the study device.

The following side effects have been seen in studies of RIC:

- Local pain or discomfort in the arm while the cuff is inflated
- Transient colour change, numbness, or tingling in the arm while the cuff is inflated
- A rash with some red dots where the cuff was inflating

The following side effects have **not** been observed in studies of RIC and are **not** expected to occur in this study, but could occur in theory. **If any of these side effects occur please stop RIC sessions immediately and call your study doctor:**

- Local swelling of the arm that continues well beyond the end of the RIC session
- Redness or paleness of the arm that continues well beyond the end of the RIC session
- Coldness of the arm that continues well beyond the end of the RIC session
- Tenderness or loss of sensation in the arm that continues well beyond the end of the RIC session
- Breakdown of the skin in the area where the cuff is placed
- Any other skin lesions in the area where the cuff is placed
- Chest pain or shortness of breath
- Diagnosis of Pulmonary Embolism (PE, lung clot) or Deep Vein Thrombosis (DVT, arm vein clot) by a healthcare provider

This is not a complete list of side effects. If you experience any unexpected effects during the study, you should contact study staff immediately (Do not wait for the next study visit.)

You should discuss these risks with the study doctor. Ask the study doctor if you have questions about the signs or symptoms of any side effects you read about in this consent form.

**Potential Interactions with Other Medications:** You can continue to take all you regular medications while on RIC. However, if you are on therapeutic **anticoagulation** (blood being greatly thinned with medications like warfarin, dabigatran, rivaroxaban, apixaban, heparin, enoxaparin, dalteparin) then as a precautionary measure you will not be included in the study. If you are started on therapeutic anticoagulation during the course of the study, please get in touch right away (see contact number below).

**Blood draw risks:**
The study doctor or study staff will take your blood by inserting a needle in your arm. Some problems you might have from this are:

- It may hurt.
- You may get a bruise.
- You may feel dizzy.
- You may get an infection.

**MRI risks:**
Some people may experience anxiety while they are in the scanner due to banging sounds from the machine or the small space. This is why we will ask you to wear earplugs. Some people may feel a little "closed-in" while inside the machine, but patients are able to speak with someone at all times and can stop the test at anytime. Some discomfort may arise from maintaining the same position throughout the session. You will be made as comfortable as possible using knee support, pillows, and blanket. You are free to discontinue the study, if you feel uncomfortable. There is also a risk of injury if metal is brought into the imaging room, which might be pulled into the MRI magnet. People with pacemakers, aneurysm clips, artificial heart valves, ear implants or metal/foreign objects in their eyes are not permitted to have an MRI. **Please tell the study doctor if you have any such implants.**

If there are incidental findings on your MRI that in the opinion of the study doctor may be considered clinically significant, this will be discussed with you and your family doctor, including options for further actions.

**Cognitive Assessment risks:**
The pencil and paper tests used in cognitive testing can take up to 1 hour to complete and may be tiring. You can request a break any time you feel you need one.

If the study investigator learns any new information regarding the risks involved, or any other finding or change to the study that might affect your willingness to continue in the study, you will be told about it.

## WILL I BENEFIT IF I TAKE PART?

If you agree to take part in this study, there may or may not be direct benefit to you. We hope the information learned from this study will benefit people with vascular cognitive impairment in the future.

## DO I HAVE TO PARTICIPATE?

Your participation in this study is strictly voluntary. If you decide not to participate it will not affect your other medical care in any way.

The investigators can remove you from the study at any time, even if you want to stay in the study. This could happen if:

- The study investigator believes it is best for you to stop being in the study
- You do not follow the study directions
- The sponsor stops funding the study for any reason

You can stop participating at any time. However, if you decide to stop participating in the study, we encourage you to talk to the study team. To help you leave the study safely, the study doctor may ask you to complete some tests. Your decision will be honored and will be discussed with your Substitute Decision Maker (SDM).

## WILL I BE PAID FOR PARTICIPATING, OR DO I HAVE TO PAY FOR ANYTHING?

You will not be compensated for your participation in this study. However, you and your caregiver will be reimbursed for parking expenses for each study visit.

There is no cost to you for the study visits or tests that are part of the study. In addition, you do not have to pay for RIC study device – it will be provided to you for the duration of the study. At the end of the study, you will be asked to return the device.

## WILL MY RECORDS BE KEPT PRIVATE?

Any of your personal information (information about you and your health that identifies you as an individual) collected or obtained, whether you choose to participate or not, will be kept confidential and protected to the fullest extent of the law. All personal information collected will be kept in a secure location. All computers used to hold information will be encrypted as per University of Calgary policy. The data for this study will be retained for 25 years.

You have the right to have any information about you and your health that is collected, used or disclosed for this study to be handled in a confidential manner.

If you decide to participate in this study, the investigator(s) and study staff will look at your personal health information and collect only the information they need for this study. Personal health information is health information about you that could identify you because it includes information such as your;

- name,
- address
- telephone number,
- date of birth,
- new and existing medical records, or
- the types, dates and results of various tests and procedures.

You have the right to access, review and request changes to your personal health information.

Access to your personal health information will take place under the supervision of the Principal Investigator.

“Study data" is health information about you that is collected for the study, but that does not directly identify you. Any study data about you that is sent outside of the hospital will have a code and will not contain your name or address, or any information that directly identifies you.

Your full date of birth will be included on all images (i.e. MRI scans) disclosed outside the institution for the purpose of the study.

Study data that is sent outside of the hospital will be used for the research purposes explained in this consent form. As part of a movement to more open science, researchers now share the information collected in their studies with each other. This will include your study data, but not any of your personal health information. The study data may be placed on websites such as the University of Calgary PRISM Dataverse (https://libanswers.ucalgary.ca/faq/164924).

The investigator(s), study staff and the other people listed above will keep the information they see or receive about you confidential, to the extent permitted by applicable laws. Even though the risk of identifying you from the study data is very small, it can never be completely eliminated.

The study staff, the Conjoint Health Research Ethics Board at the University of Calgary, the monitor(s), and the regulatory authority (Health Canada) will have access to your personal information for purposes associated with the study, but will only be allowed to access your records under the supervision of the Principal Investigator and will be obligated to protect your privacy and not disclose your personal information. None of your personal information will be given to anyone without your permission unless required by law. When the results of this study are published, your identity will not be disclosed. Even though the risk of identifying you from the study data is very small, it can never be completely eliminated.

Authorized representatives from the University of Calgary and the Conjoint Health Research Ethics Board may look at your identifiable medical/clinical study records held at the University of Calgary for quality assurance purposes.

When the results of this study are published, your identity will not be disclosed.

You have the right to be informed of the results of this study once the entire study is complete.

A description of this clinical trial will be available on *http://www.ClinicalTrials.gov*, as required by U.S. Law. This website will not include information that can identify you. At most, the website will include a summary of the results of all participants. You can search this website at any time.

## IF I SUFFER A RESEARCH-RELATED INJURY, WILL I BE COMPENSATED?

You may contact the individuals listed at the beginning of this consent form at any time for treatment of side effects, questions, emergencies or FOR ANY OTHER REASON. In the event that you suffer injury as a result of participating in this research, no compensation will be provided to you by the University of Calgary, Alberta Health Services or the Researchers. Nonetheless, you still have all your legal rights. Nothing said in this consent form alters your right to seek damages.

All participants in a research study have the following rights:

1. You have the right to have this form and all information concerning this study explained to you and if you wish translated into your preferred language.

2. Participating in this study is your choice *(voluntary)*. You have the right to refuse to participate, or to stop participating in this study at any time without having to provide a reason. If you choose to withdraw, it will not have any effect on your future medical treatment or health care. Should you choose to withdraw from the study you are encouraged to contact individuals listed at the beginning of this consent form.

3. You have the right to receive all significant information that could help you make a decision about participating in this study. You also have the right to ask questions about this study and your rights as a research participant, and to have them answered to your satisfaction, before you make any decision. You also have the right to ask questions and to receive answers throughout this study. If you have any questions about this study you may contact the person in charge of this study at your centre (Principal Investigator), Dr. Eric Smith at 403-944-1594.

4. By signing this consent form, you do not give up any of your legal rights.

5. You have the right to receive a copy of this signed and dated informed consent package before participating in this study.

6. You have the right to be told about any new information that might reasonably affect your willingness to continue to participate in this study as soon as the information becomes available to the study staff. This may include new information about the risks and benefits of being a participant in this study.

7. If you become sick or injured as a direct result of your participation in this study, your medical care will be provided. Please contact the study doctor if you feel you have been injured as a result of this study.

8. If, as a result of your participation in this study, any new clinically important medical information about your health is obtained, you will be given the opportunity to decide whether you wish to be made aware of that information.

9. You have the right to access, review and request changes to your personal information (i.e. address, date of birth).

10. You have the right to be informed of the results of this study once the entire study is complete.

11. For medical emergencies, proceed to the emergency room of the nearest hospital and contact study personnel as soon as possible. All adverse events should be reported to Dr. Eric Smith at 403-944-1594 as soon as possible. **In case of an adverse event or to reach the study physician for urgent matters, please contact the Foothills Hospital locating number 403-944-1110 and ask for Dr. Eric Smith to be paged. This is a 24-hour emergency contact number.**

# SIGNATURES

*The role of the caregiver as the participant's study partner is explained on pages 15 and 16 of the consent form, and the caregiver will separately consent to these duties on page 16.*

## Participant

By signing this form, I confirm that:

- This research study has been fully explained to me and all of my questions answered to my satisfaction
- I understand the requirements of participating in this research study
- I have been informed of the risks and benefits, if any, of participating in this research study
- I have been informed of any alternatives to participating in this research study
- I have been informed of the rights of research participants
- I have read each page of this form
- I authorize access to my personal health information (medical record) and research study data as explained in this form
- I have agreed to participate in this study or agree to allow the person I am responsible for to participate in this study

Your signature on this form indicates that you have understood the information regarding your participation in the research project and agree to participate as a subject. In no way does this waive your legal rights nor release the investigators, or involved institutions from their legal and professional responsibilities. You are free to withdraw from the study without jeopardizing your health care. You may withdraw from the study at any time, without need to provide a reason, by contacting the Principal Investigator Dr. Eric Smith. Samples and data may be withdrawn up until the point that they are accessed by external researchers. Once coded samples or data are sent to approved researchers, they can no longer be withdrawn from the study.

If you have further questions concerning matters related to this research, please contact the Principal Investigator, Dr. Eric Smith at (403) 944-1594 or (403) 210-7611.

If you have any questions concerning your rights as a possible participant in this research, please contact the Chair, Conjoint Health Research Ethics Board, University of Calgary at 403-220-7990.

| Participant's Name | Signature | Date (!!"####"$$) |
|---|---|---|
| Investigator Name | Signature | Date (!!"####"$$) |
| Witness' Name | Signature | Date (!!"####"$$) |

The University of Calgary Conjoint Health Research Ethics Board has approved this research study.

A signed copy of this consent form has been given to you to keep for your records and reference.

## STUDY PARTNER INFORMATION

I understand that _____, a patient with vascular cognitive impairment whom I know well and for whom I am/will be a caregiver, has consented to be a research subject in the TRIC-VCI study. This study is examining whether different doses or schedules of Remote Ischemic pre-Conditioning have any advantage over each in other slowing cognitive or brain changes in patients with vascular cognitive impairment. I have read and understand the consent form that he/she has signed. I understand that in order for this study to be conducted in the most valuable manner possible, I will have the following responsibilities during the time that the patient remains in this study:

1. I will accompany the patient to all clinic visits.

2. I will ensure that the patient keeps all study appointments (phone or in-person) as listed in the schedule that I will receive. I will provide information about how the patient is doing when I bring him/her in for clinic visits and complete the necessary caregiver/informant questionnaires, and provide information if I'm contacted by telephone as per the predefined schedule.

3. If any severe, serious, or unexpected event occurs to the patient between clinic visits, I will immediately call the Study Doctor or his/her representative to report it, whether or not I or the patient thinks that it might be due to the study treatment. I will follow all instructions the Study Doctor or his/her representative gives me at that time.

If for any reason I become unable to fulfill these responsibilities, I will notify the Study Doctor immediately. I understand that I may be asked to find someone else to take over these responsibilities for whatever time I am unavailable. If this is not possible, I understand that it might be necessary to discontinue the patient's participation in the study.

For this study, I am aware that the study physician will need to document in the patient's chart that I am his/her study partner/caregiver, and certain information will be collected from me such as my contact information.

I am also aware that the information collected as part of this study will be kept confidential unless release is required by law, and only used for the purpose of the research study as stated in the study objectives above.

## DOCUMENTATION OF STUDY PARTNER CONSENT

I have read this document/had its contents explained to me and understand the purpose of this study and what the participation of the patient for whom I provide care will involve. I agree to assist the patient in the study for the entire duration of the trial and to attend the visits as required.

| _____ | _____ | _____ |
|---|---|---|
| Caregiver's Name | Signature | Date (*DD/MM/YY*) |

The University of Calgary Conjoint Health Research Ethics Board has approved this research study.
A signed copy of this consent form has been given to you to keep for your records and reference.

CRU #044 TRIC VCI Plate #001 Screening

**Subject ID:** Centre Subject ID **Date:** yyyy mm dd

## SCREENING *(page 1 of 6)*

| | |
|---|---|
| Has the research candidate and their study partner given informed consent and signed the consent forms? | ☐ Yes ☐ No |

| INCLUSION CRITERIA: All responses must be YES to qualify: | | |
|---|---|---|
| Criterion | Operationalized as: | Determination |
| Age 60-85 | N/A | ☐ Yes ☐ No |
| Independent with basic activities | BADLS question 2 response a) selected | ☐ Yes ☐ No |
| | BADLS question 4 response a) selected | ☐ Yes ☐ No |
| | BADLS question 5 response a) selected | ☐ Yes ☐ No |
| | BADLS question 6 response a) selected | ☐ Yes ☐ No |
| | BADLS question 7 response a) selected | ☐ Yes ☐ No |
| | BADLS question 8 response a) selected | ☐ Yes ☐ No |
| | BADLS question 9 response a) selected | ☐ Yes ☐ No |
| | BADLS question 14 response a) selected | ☐ Yes ☐ No |
| Cognitive impairment | MoCA total score 24 or lower | ☐ Yes ☐ No |
| Cognitive concern | EITHER 2 or more positive responses on AD8<br>OR<br>Clinician judgement based on history | ☐ Yes ☐ No |
| Evidence of cerebral small vessel disease | EITHER 2 or more supratentorial subcortical infarcts<br>OR<br>Beginning confluent or confluent WMH on modified AR-WMC scale on CT or MRI | ☐ Yes ☐ No |

CRU #044 TRIC VCI Plate #002 Screening

**Subject ID:** Centre Subject ID **Date:** yyyy mm dd

## SCREENING *(page 2 of 6)*

| EXCLUSION CRITERIA: All responses must be NO to qualify: | |
|---|---|
| **Criterion** | **Determination** |
| Large cortical infarcts (>10mm) | ☐ Yes ☐ No |
| Neuroimaging evidence of mass lesion, intracerebral hemorrhage, vascular malformation, or evidence non-vascular disease such as hydrocephalus | ☐ Yes ☐ No |
| Resides in a long term care facility | ☐ Yes ☐ No |
| Other significant neurological or psychiatric disease (e.g. multiple sclerosis) | ☐ Yes ☐ No |
| Subject does not have a study partner who can provide corroborative information | ☐ Yes ☐ No |
| English or French is not sufficiently proficient for clinical assessment and neuropsychological testing | ☐ Yes ☐ No |
| Total score on the MoCA 12 or lower | ☐ Yes ☐ No |
| Unable to undergo MRI due to medical contraindications such a cardiac pacemaker, or inability to tolerate the procedure | ☐ Yes ☐ No |
| Co-morbid medical illness that in the judgment of the study investigator makes it unlikely that the participant will be able to complete one year of study follow-up | ☐ Yes ☐ No |
| On therapeutic anticoagulation with doses used for treatment of deep venous thrombosis, pulmonary embolism, or for stroke prevention in atrial fibrillation | ☐ Yes ☐ No |
| Significant bleeding diathesis | ☐ Yes ☐ No |
| Any symptomatic or previously known arm soft-tissue disease, vascular injury, or peripheral vascular disease (PVD) | ☐ Yes ☐ No |
| Hypertension with systolic blood pressure >=180 mmHg despite medical treatment at the time of enrolment | ☐ Yes ☐ No |
| Planned revascularization (any angioplasty or vascular surgery) within the next 3 months | ☐ Yes ☐ No |
| Planned surgical procedure within the next 3 months | ☐ Yes ☐ No |
| Currently receiving an investigational drug or device by other studies | ☐ Yes ☐ No |

*Signature of investigator confirms the Inclusion/Exclusion Criteria :* _____

***e-signature***
***iDataFax use only***

hh : mm yyyy mm dd

PI's printed first and last name: _____

CRU #044 TRIC VCI Plate #003 Screening

**Subject ID:** ☐☐ ☐☐☐ *Centre* *Subject ID*

**Date:** ☐☐☐☐ ☐☐ ☐☐ *yyyy* *mm* *dd*

## SCREENING *(page 3 of 6)*

| DEMOGRAPHICS | |
|---|---|
| 1. Age: | ☐☐ |
| 2. Sex: | ☐ Male ☐ Female |
| 3. Mother tongue (first language learned): | ☐ English ☐ French<br>☐ Other: _____ |
| 4. Marital Status: | ☐ Single ☐ Separated<br>☐ Married ☐ Divorced<br>☐ Common-law partnership ☐ Widowed |
| 5. Current living circumstance: | ☐ House or apartment/condominium that you own<br>☐ Apartment/condominium or house that you rent<br>☐ Retirement home (autonomous living)<br>☐ Residence for semi-autonomous individuals<br>☐ Nursing home or long-term care (assisted living)<br>☐ Other, please specify: _____ |
| 6. What is the highest grade or level of school completed or highest degree obtained: | ☐ Never attended school<br>☐ Some primary/grade school<br>☐ Completed primary/grade school<br>☐ Some high school<br>☐ Completed high school<br>☐ Apprenticeship<br>☐ Technical school or community college<br>☐ CEGEP<br>☐ Undergraduate degree at university (e.g., B.A, B.SC, B.Eng., LL.B., B.Ed., etc)<br>☐ Some graduate (post-undergraduate) school<br>☐ Graduate degree at university |

CRU #044 TRIC VCI Plate #004 Screening

**Subject ID:** Centre Subject ID **Date:** yyyy mm dd

## SCREENING *(page 4 of 6)*

| DEMOGRAPHICS | |
|---|---|
| 7. Study informant relationship to patient: | ☐ Spouse ☐ Child ☐ Parent ☐ Friend ☐ Other: _____ |
| 8. Informant frequency of contact with patient: | ☐ Daily ☐ One or more times per week ☐ One or more times per month ☐ Less than once per month |

CRU #044 TRIC VCI Plate #005 Screening

**Subject ID:** ☐☐ ☐☐☐ (Centre / Subject ID) **Date:** ☐☐☐☐ ☐☐ ☐☐ (yyyy / mm / dd)

## SCREENING *(page 5 of 6)*

| MEDICAL HISTORY | |
|---|---|
| 1. History of prior transient ischemic attack: | ☐ Yes ☐ No |
| If yes, then complete 1.a. and 1.b. | |
| 1.a. Is there a history of more than one prior transient ischemic attack? | ☐ Yes ☐ No |
| 1.b. What was the month and year of the most recent prior transient attack? | ☐☐☐☐ (yyyy) ☐☐ (mm) |
| 2. History of prior stroke: | ☐ Yes ☐ No |
| If yes, then complete 2.a and 2.b. | |
| 2.a. Is there a history of more than one prior stroke? | ☐ Yes ☐ No |
| 2.b. What was the month and year of the most recent prior stroke? | ☐☐☐☐ (yyyy) ☐☐ (mm) |
| 3. History of carotid stenosis: | ☐ Yes ☐ No |
| 4. History of prior carotid revascularization: | ☐ Yes ☐ No |
| 4.a. Side of carotid revascularization: | ☐ R ☐ L ☐ Both |
| 5. History of hypertension or use of antihypertensive medications to control blood pressure: | ☐ Yes ☐ No |
| 6. History of diabetes mellitus: | ☐ Yes ☐ No |
| 7. History of dyslipidemia or use of antilipid medications: | ☐ Yes ☐ No |
| 8. History of myocardial infarction: | ☐ Yes ☐ No |
| 9. History of angina: | ☐ Yes ☐ No |
| [illegible] | ☐ Yes ☐ No |
| 11. History of heart failure: | ☐ Yes ☐ No |

CRU #044 TRIC VCI Plate #006 Screening

**Subject ID:** | | | | | | Centre | Subject ID |

**Date:** | | | | | | | | yyyy | mm | dd |

## SCREENING *(page 6 of 6)*

| MEDICAL HISTORY | | |
|---|---|---|
| 12. History of peripheral vascular disease: | ☐ Yes | ☐ No |
| 13. History of prior deep venous thrombosis: | ☐ Yes | ☐ No |
| 14. History of prior cancer: | ☐ Yes | ☐ No |
| 15. History of any other central nervous system diseases (list): _____ _____ | | |

CRU #044 TRIC VCI Plate #007

☐ Screening ☐ Randomization

☐ Follow Up ☐ End

**Subject ID:** ☐☐ ☐☐☐ (Centre / Subject ID)

**Date:** ☐☐☐☐ ☐☐ ☐☐ (yyyy / mm / dd)

# MEDICATIONS

| | |
|---|---|
| 1. Is the patient taking an antiplatelet drug? | ☐ Yes ☐ No |
| If yes, please answer 1.a. below: | |
| 1.a. Antiplatelet drug class(es)—select all that apply: ☐ Acetylsalicylic acid (e.g. Aspirin) ☐ Clopidogrel (Plavix) ☐ Aggrenox ☐ Persantine ☐ Ticagrelor (Brilinta) ☐ Prasugrel (Effient) | |
| 2. Is the patient taking an anticoagulant drug? | ☐ Yes ☐ No |
| 2.a. If yes, is the drug taken at doses used for treatment of deep venous thrombosis, pulmonary embolism, or for stroke prevention in atrial fibrillation? | ☐ Yes ☐ No |

3. For all other medications, please complete "Medications List" form(s).

Signature: _____ Date: ☐☐☐☐ ☐☐ ☐☐ (yyyy / mm / dd)

CRU #044 TRIC VCI Plate #008

☐ Screening ☐ Randomization ☐ Follow Up

**Subject ID:** ☐☐ ☐☐☐ (Centre / Subject ID) **Date:** ☐☐☐☐ ☐☐ ☐☐ (yyyy / mm / dd)

# PHYSICAL EXAMINATION

| PHYSICAL MEASUREMENTS MUST BE PERFORMED BY STUDY PERSONNEL BLINDED TO TREATMENT ASSIGNMENT | | | |
|---|---|---|---|
| 1. Blood pressure (seated) | | | |
| 1.a. Right arm systolic blood pressure: ☐☐☐ **mmHg** | | 1.c. Left arm systolic blood pressure: ☐☐☐ **mmHg** | |
| 1.b. Right arm diastolic blood pressure: ☐☐☐ **mmHg** | | 1.d. Left arm diastolic blood pressure: ☐☐☐ **mmHg** | |

| 2. Arm examination: | | | | |
|---|---|---|---|---|
| | RIGHT | | LEFT | |
| Radial pulse palpable | ☐ Yes | ☐ No | ☐ Yes | ☐ No |
| Ulnar pulse palpable | ☐ Yes | ☐ No | ☐ Yes | ☐ No |
| Brachial pulse palpable | ☐ Yes | ☐ No | ☐ Yes | ☐ No |
| Local edema | ☐ Yes | ☐ No | ☐ Yes | ☐ No |
| Skin breakdown | ☐ Yes | ☐ No | ☐ Yes | ☐ No |
| Rash | ☐ Yes | ☐ No | ☐ Yes | ☐ No |
| Petechiae | ☐ Yes | ☐ No | ☐ Yes | ☐ No |
| Upper arm tenderness | ☐ Yes | ☐ No | ☐ Yes | ☐ No |
| Lower arm tenderness | ☐ Yes | ☐ No | ☐ Yes | ☐ No |

3. Arm examination comments:

_____

_____

_____

| 4. Examiner blinded to treatment arm: | ☐ Yes | ☐ No |
|---|---|---|

Signature: _____ Date: ☐☐☐☐ ☐☐ ☐☐ (yyyy / mm / dd)

CRU #044 TRIC VCI Plate #009

☐ Screening ☐ Randomization

☐ Follow Up ☐ End

**Subject ID:** ☐☐ ☐☐☐ (Centre / Subject ID)

**Date:** ☐☐☐☐ ☐☐ ☐☐ (yyyy / mm / dd)

## NIH STROKE SCALE *(page 1 of 3)*

| | | |
|---|---|---|
| 1a. Level of Consciousness | ☐ | 0 - Alert |
| | ☐ | 1 - Not alert, but arousable with minimal stimulation |
| | ☐ | 2 - Not alert, requires repeated stimulation to attend |
| | ☐ | 3 - Coma |
| 1b. LOC Questions *Ask patient the month and their age* | ☐ | 0 - Answers both correctly |
| | ☐ | 1 - Answers one correctly |
| | ☐ | 2 - Both incorrect |
| 1c. LOC Commands *Ask patient to open/close eyes and form/release fst* | ☐ | 0 - Obeys both correctly |
| | ☐ | 1 - Obeys one correctly |
| | ☐ | 2 - Both incorrect |
| 2. Best Gaze *Only horizontal eye movement* | ☐ | 0 - Normal |
| | ☐ | 1 - Partial gaze palsy |
| | ☐ | 2 - Forced gaze palsy |
| 3. Visual Field Testing | ☐ | 0 - No visual field loss |
| | ☐ | 1 - Partial hemianopia |
| | ☐ | 2 - Complete hemianopia |
| | ☐ | 3 - Bilateral hemianopia (blind, incl. Cortical blindness) |
| 4. Facial Palsy *Ask patient to show teeth or raise eyebrows and close eyes tightly* | ☐ | 0 - Normal symmetrical movement |
| | ☐ | 1 - Minor paralysis (flattened nasolabial fold, asymmetry on smiling) |
| | ☐ | 2 - Partial paralysis (total or near total paralysis of lower face) |
| | ☐ | 3 - Complete paralysis of one or both sides (absence of facial movement in the upper and lower face) |

CRU #044 TRIC VCI Plate #010

☐ Screening ☐ Randomization
☐ Follow Up ☐ End

**Subject ID:** ☐☐ ☐☐☐ (Centre / Subject ID) **Date:** ☐☐☐☐ ☐☐ ☐☐ (yyyy / mm / dd)

## NIH STROKE SCALE *(page 2 of 3)*

| | L | R | |
|---|---|---|---|
| 5. Motor Function Arm | ☐ | ☐ | 0 - Normal (extends arm 90º or 45º for 10 sec without drift) |
| | ☐ | ☐ | 1 - Drift |
| | ☐ | ☐ | 2 - Some effort against gravity |
| | ☐ | ☐ | 3 - No effort against gravity |
| | ☐ | ☐ | 4 - No movement |
| | ☐ | ☐ | 9 - Untestable (Joint fused/limb amputated) (*do not add score*) |

| | L | R | |
|---|---|---|---|
| 6. Motor Function Leg | ☐ | ☐ | 0 - Normal (holds leg in 30º position for 5 sec without drift) |
| | ☐ | ☐ | 1 - Drift |
| | ☐ | ☐ | 2 - Some effort against gravity |
| | ☐ | ☐ | 3 - No effort against gravity |
| | ☐ | ☐ | 4 - No movement |
| | ☐ | ☐ | 9 - Untestable (Joint fused/limb amputated) (*do not add score*) |

| | | |
|---|---|---|
| 7. Limb ataxia | ☐ | 0 - No ataxia |
| | ☐ | 1 - Present in one limb |
| | ☐ | 2 - Present in two limbs |

| | | |
|---|---|---|
| 8. Sensory *Use pinprick to test arms, legs, trunk and face, compare side to side* | ☐ | 0 - Normal |
| | ☐ | 1 - Mild to moderate decrease in sensation |
| | ☐ | 2 - Severe to total sensory loss |

| | | |
|---|---|---|
| 9. Best Language *Ask patient to describe picture, name items* | ☐ | 0 - No aphasia |
| | ☐ | 1 - Mild to moderate aphasia |
| | ☐ | 2 - Severe aphasia |
| | ☐ | 3 - Mute |

CRU #044 TRIC VCI Plate #011

☐ Screening ☐ Randomization

☐ Follow Up ☐ End

**Subject ID:** ☐☐ ☐☐☐ (Centre / Subject ID)

**Date:** ☐☐☐☐ ☐☐ ☐☐ (yyyy / mm / dd)

## NIH STROKE SCALE *(page 3 of 3)*

| | | |
|---|---|---|
| I0. Dysarthria *Ask patient to read several words* | ☐ | 0 - No aphasia |
| | ☐ | 1 - Mild to moderate slurring of words |
| | ☐ | 2 - Near unintelligible or unable to speak |
| | ☐ | 9 - Intubated or other physical barrier (*do not add score*) |
| 11. Extinction and Inattention *Use visual double stimulation or sensory double stimulation* | ☐ | 0 - Normal |
| | ☐ | 1 - Inattention or extinction to bilateral simultaneous stimulation in one of the sensory modalities |
| | ☐ | 2 - Hemi-inattention, severe or to more than one modality |
| Auto-Calculated Total Score Only: ☐☐ [range 0-42] | | |

Signature: _____ Date: ☐☐☐☐ ☐☐ ☐☐ (yyyy / mm / dd)

CRU #044 TRIC VCI Plate #012 Screening

**Subject ID:** Centre Subject ID **Date:** yyyy mm dd

# HACHINSKI ISCHEMIC SCORE

| Characteristic | YES | NO |
|---|---|---|
| Abrupt onset | ☐ 2 | ☐ 0 |
| Stepwise deterioration | ☐ 1 | ☐ 0 |
| Fluctuating course | ☐ 2 | ☐ 0 |
| Nocturnal confusion | ☐ 1 | ☐ 0 |
| Preservation of personality | ☐ 1 | ☐ 0 |
| Depression | ☐ 1 | ☐ 0 |
| Somatic complaints | ☐ 1 | ☐ 0 |
| Emotional lability | ☐ 1 | ☐ 0 |
| History of hypertension | ☐ 1 | ☐ 0 |
| History of stroke | ☐ 2 | ☐ 0 |
| Associated atherosclerosis | ☐ 1 | ☐ 0 |
| Focal neurological symptoms | ☐ 2 | ☐ 0 |
| Focal neurological signs | ☐ 2 | ☐ 0 |

Auto-Calculated Total Score Only: ☐☐ [range 0-18]

Signature: _____ Date: yyyy mm dd

CRU #044 TRIC VCI Plate #013

☐ Screening ☐ Randomization

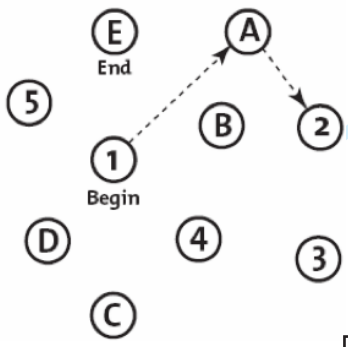
☐ Follow Up ☐ End

**Subject ID:** ☐☐ ☐☐☐ (Centre / Subject ID)

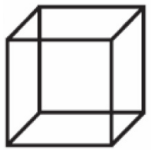
**Date:** ☐☐☐☐ ☐☐ ☐☐ (yyyy / mm / dd)

# MONTREAL COGNITIVE ASSESSMENT *(page 1 of 2)*

## VISUOSPATIAL / EXECUTIVE




☐



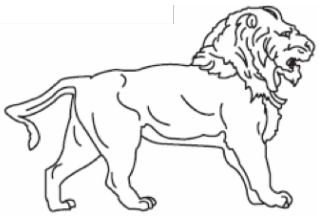

☐

Draw CLOCK (Ten past eleven)
(3 points)

☐ Contour ☐ Numbers ☐ Hands

**POINTS** ☐ /5

## NAMING



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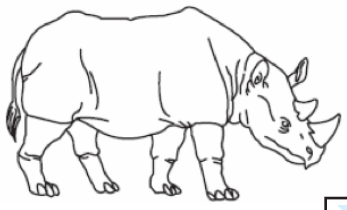
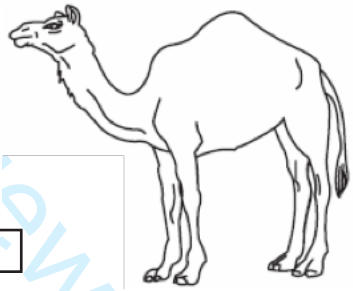


☐



☐

☐ /3

## MEMORY

Read list of words, subject must repeat them. Do 2 trials. Do a recall after 5 minutes.

| | FACE | VELVET | CHURCH | DAISY | RED |
|---|---|---|---|---|---|
| 1st trial | ☐ | ☐ | ☐ | ☐ | ☐ |
| 2nd trial | ☐ | ☐ | ☐ | ☐ | ☐ |

No Points

## ATTENTION

Read list of digits (1 digit/sec).

Subject has to repeat them in the forward order ☐ 2 1 8 5 4

Subject has to repeat them in the backward order ☐ 7 4 2

☐ /2

Read list of letters. The subject must tap with his hand at each letter A. No points if ≥ 2 errors

☐ F B A C M N A A J K L B A F A K D E A A A J A M O F A A B

☐ /1

Serial 7 subtraction starting at 100 ☐ 93 ☐ 86 ☐ 79 ☐ 72 ☐ 65

4 or 5 correct subtractions: **3 pts**, 2 or 3 correct: **2 pts**, 1 correct: **1 pt**, 0 correct: **o pt**

☐ /3

CRU #044 TRIC VCI Plate #014

☐ Screening ☐ Randomization
☐ Follow Up ☐ End

**Subject ID:** ☐☐ ☐☐☐ (Centre / Subject ID) **Date:** ☐☐☐☐ ☐☐ ☐☐ (yyyy / mm / dd)

# MONTREAL COGNITIVE ASSESSMENT *(page 2 of 2)*

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| LANGUAGE | Repeat: I only know that John is the one to help today. ☐<br>The cat always hid under the couch when dogs were in the room ☐ | | | | | | | ☐☐ /2 |
| Fluency / Name maximum number of words in one minute that begin with the letter F ☐ _____ (N ≥ 11 words) | | | | | | | | ☐☐ /1 |
| ABSTRACTION | Similarity between e.g. banana - orange = fruit ☐ train - bicycle ☐ watch - ruler | | | | | | | ☐☐ /2 |
| DELAYED RECALL | Has to recall words WITH NO CUE | FACE ☐ | VELVET ☐ | CHURCH ☐ | DAISY ☐ | RED ☐ | Points for UNCUED recall only | ☐☐ /5 |
| Optional | Category cue | ☐ | ☐ | ☐ | ☐ | ☐ | | |
| | Multiple choice cue | ☐ | ☐ | ☐ | ☐ | ☐ | | |
| ORIENTATION | ☐ Date ☐ Month ☐ Year ☐ Day ☐ Place ☐ City | | | | | | | ☐☐ /6 |
| Normal ≥ 26 / 30 | | | | | | | **Auto-Calculated Total Only** | ☐☐ /30 |

Administered by: _____

Signature: _____ Date: ☐☐☐☐ ☐☐ ☐☐ (yyyy / mm / dd)

CRU #044 TRIC VCI Plate #015

☐ Screening ☐ Randomization
☐ Follow Up ☐ End

**Subject ID:** ☐☐ ☐☐☐ (Centre / Subject ID)

**Date:** ☐☐☐☐ ☐☐ ☐☐ (yyyy / mm / dd)

# INFORMANT BRISTOL ACTIVITIES OF DAILY LIVING SCALE *(page 1 of 6)*

This questionnaire is designed to reveal the everyday ability of people who have memory difficulties of one form or another.

For each activity (No. 1 - 20), statements a - e refer to a different level of ability.

Thinking of the last 2 weeks, tick the box that represents your relative's/friend's AVERAGE ability. (If in doubt about which box to tick, choose the level of ability which represents their average performance over the last 2 Weeks. Tick 'Not applicable' if your relative never did that activity when they were well).

| | | |
|---|---|---|
| 1. PREPARING FOOD | ☐ | a) Selects and prepares food as required |
| | ☐ | b) Able to prepare food if ingredients set out |
| | ☐ | c) Can prepare food if prompted step by step |
| | ☐ | d) Unable to prepare food even with prompting and supervision |
| | ☐ | e) Not applicable |
| 2. EATING | ☐ | a) Eats appropriately using correct cutlery |
| | ☐ | b) Eats appropriately if food made manageable and/or uses spoon |
| | ☐ | c) Uses fingers to eat food |
| | ☐ | d) Needs to be fed |
| | ☐ | e) Not applicable |
| 3. PREPARING DRINK | ☐ | a) Selects and prepares drinks as required |
| | ☐ | b) Can prepare drinks if ingredients left available |
| | ☐ | c) Can prepare drinks if prompted step by step |
| | ☐ | d) Unable to make a drink even with prompting and supervision |
| | ☐ | e) Not applicable |

CRU #044 TRIC VCI Plate #016

☐ Screening ☐ Randomization
☐ Follow Up ☐ End

**Subject ID:** ☐☐ ☐☐☐ (Centre / Subject ID) **Date:** ☐☐☐☐ ☐☐ ☐☐ (yyyy / mm / dd)

# INFORMANT BRISTOL ACTIVITIES OF DAILY LIVING SCALE *(page 2 of 6)*

| | | |
|---|---|---|
| 4. DRINKING | ☐ | a) Drinks appropriately |
| | ☐ | b) Drinks appropriately with aids, beaker/straw etc. |
| | ☐ | c) Does not drink appropriately even with aids but attempts to |
| | ☐ | d) Has to have drinks administered (fed) |
| | ☐ | e) Not applicable |
| 5. DRESSING | ☐ | a) Selects appropriate clothing and dresses self |
| | ☐ | b) Puts clothes on in wrong order and/or back to front and/or dirty clothing |
| | ☐ | c) Unable to dress self but moves limbs to assist |
| | ☐ | d) Unable to assist and requires total dressing |
| | ☐ | e) Not applicable |
| 6. HYGIENE | ☐ | a) Washes regularly and independently |
| | ☐ | b) Can wash self if given soap, flannel, towel, etc. |
| | ☐ | c) Can wash self if prompted and supervised |
| | ☐ | d) Unable to wash self and needs full assistance |
| | ☐ | e) Not applicable |
| 7. TEETH | ☐ | a) Cleans own teeth/dentures regularly and independently |
| | ☐ | b) Cleans teeth/dentures if given appropriate items |
| | ☐ | c) Requires some assistance, toothpaste on brush, brush to mouth etc. |
| | ☐ | d) Full assistance given |
| | ☐ | e) Not applicable |

CRU #044 TRIC VCI Plate #017

☐ Screening ☐ Randomization
☐ Follow Up ☐ End

**Subject ID:** ☐☐ ☐☐☐ (Centre / Subject ID) **Date:** ☐☐☐☐ ☐☐ ☐☐ (yyyy / mm / dd)

## INFORMANT BRISTOL ACTIVITIES OF DAILY LIVING SCALE *(page 3 of 6)*

| | | |
|---|---|---|
| 8. BATH/SHOWER | ☐ | a) Bathes regularly and independently |
| | ☐ | b) Needs bath to be drawn/shower turned on but washes independently |
| | ☐ | c) Needs supervision and prompting to wash |
| | ☐ | d) Totally dependent, needs full assistance |
| | ☐ | e) Not applicable |
| 9. TOILET/COMMODE | ☐ | a) Uses toilet appropriately when required |
| | ☐ | b) Needs to be taken to the toilet and given assistance |
| | ☐ | c) Incontinent of urine or faeces |
| | ☐ | d) Incontinent of urine and faeces |
| | ☐ | e) Not applicable |
| 10. TRANSFERS | ☐ | a) Can get in/out of chair unaided |
| | ☐ | b) Can get into a chair but needs help to get out |
| | ☐ | c) Needs help getting in and out of a chair |
| | ☐ | d) Totally dependent on being put into and lifted from chair |
| | ☐ | e) Not applicable |
| 11. MOBILITY | ☐ | a) Walks independently |
| | ☐ | b) Walks with assistance i.e. furniture, arm for support |
| | ☐ | c) Uses aids to mobilise i.e. frame, sticks etc. |
| | ☐ | d) Unable to walk |
| | ☐ | e) Not applicable |

CRU #044 TRIC VCI Plate #018

☐ Screening ☐ Randomization ☐ Follow Up ☐ End

**Subject ID:** ☐☐ ☐☐☐ *Centre* *Subject ID*

**Date:** ☐☐☐☐ ☐☐ ☐☐ *yyyy* *mm* *dd*

## INFORMANT BRISTOL ACTIVITIES OF DAILY LIVING SCALE *(page 4 of 6)*

| | | |
|---|---|---|
| 12. ORIENTATION – TIME | ☐ | a) Fully orientated to time/day/date etc. |
| | ☐ | b) Unaware of time/day etc. but seems unconcerned |
| | ☐ | c) Repeatedly asks the time/day/date |
| | ☐ | d) Mixes up night and day |
| | ☐ | e) Not applicable |
| 13. ORIENTATION – SPACE | ☐ | a) Fully orientated to surroundings |
| | ☐ | b) Orientated to familiar surroundings only |
| | ☐ | c) Gets lost in home, needs reminding where bathroom is, etc. |
| | ☐ | d) Does not recognise home as own and attempts to leave |
| | ☐ | e) Not applicable |
| 14. COMMUNICATION | ☐ | a) Able to hold appropriate conversation |
| | ☐ | b) Shows understanding and attempts to respond verbally with gestures |
| | ☐ | c) Can make self-understood but difficulty understanding others |
| | ☐ | d) Does not respond to, or communicate with others |
| | ☐ | e) Not applicable |
| 15. TELEPHONE | ☐ | a) Uses telephone appropriately, including obtaining correct number |
| | ☐ | b) Uses telephone if number given verbally/visually or predialed |
| | ☐ | c) Answers telephone but does not make calls |
| | ☐ | d) Unable/unwilling to use telephone at all |
| | ☐ | e) Not applicable |

CRU #044 TRIC VCI Plate #019

☐ Screening ☐ Randomization
☐ Follow Up ☐ End

**Subject ID:** ☐☐ ☐☐☐ (Centre / Subject ID) **Date:** ☐☐☐☐ ☐☐ ☐☐ (yyyy / mm / dd)

# INFORMANT BRISTOL ACTIVITIES OF DAILY LIVING SCALE *(page 5 of 6)*

| | | |
|---|---|---|
| 16. HOUSEWORK/GARDENING | ☐ | a) Able to do housework/gardening to previous standard |
| | ☐ | b) Able to do housework/gardening but not to previous standard |
| | ☐ | c) Limited participation with a lot of supervision |
| | ☐ | d) Unwilling/unable to participate in previous activities |
| | ☐ | e) Not applicable |
| 17. SHOPPING | ☐ | a) Shops to previous standard |
| | ☐ | b) Only able to shop for 1 or 2 items with or without a list |
| | ☐ | c) Unable to shop alone, but participates when accompanied |
| | ☐ | d) Unable to participate in shopping even when accompanied |
| | ☐ | e) Not applicable |
| 18. FINANCES | ☐ | a) Responsible for own finances at previous level |
| | ☐ | b) Unable to write cheque. Can sign name & recognises money values |
| | ☐ | c) Can sign name but unable to recognise money values |
| | ☐ | d) Unable to sign name or recognise money values |
| | ☐ | e) Not applicable |

CRU #044 TRIC VCI Plate #020

☐ Screening ☐ Randomization
☐ Follow Up ☐ End

**Subject ID:** ☐☐ ☐☐☐ *Centre* *Subject ID*

**Date:** ☐☐☐☐ ☐☐ ☐☐ *yyyy* *mm* *dd*

# INFORMANT BRISTOL ACTIVITIES OF DAILY LIVING SCALE *(page 6 of 6)*

| | | |
|---|---|---|
| 19. GAMES/HOBBIES | ☐ | a) Participates in pastimes/activities to previous standard |
| | ☐ | b) Participates but needs instruction/supervision |
| | ☐ | c) Reluctant to join in, very slow needs coaxing |
| | ☐ | d) No longer able or willing to join in |
| | ☐ | e) Not applicable |

| | | |
|---|---|---|
| 20. TRANSPORT | ☐ | a) Able to drive, cycle or use public transport independently |
| | ☐ | b) Unable to drive but uses public transport or bike etc. |
| | ☐ | c) Unable to use public transport alone |
| | ☐ | d) Unable/unwilling to use transport even when accompanied |
| | ☐ | e) Not applicable |

CRU #044 TRIC VCI Plate #021 Screening

**Subject ID:** ☐☐ ☐☐☐ *Centre* *Subject ID*

**Date:** ☐☐☐☐ ☐☐ ☐☐ *yyyy* *mm* *dd*

# INFORMANT AD8 QUESTIONNAIRE

The questionnaire should be answered by a spouse, family member, friend, or caregiver. The questionnaire should be given to the respondent on a clipboard for self–administration.

| Remember, "Yes, a change" indicates that there has been a change in the last several years caused by cognitive (thinking and memory) problems. | YES, A change | NO, No change | N/A, Don't know |
|---|---|---|---|
| 1. Problems with judgment (e.g., problems making decisions, bad financial decisions, problems with thinking) | ☐ | ☐ | ☐ |
| 2. Less interest in hobbies/activities | ☐ | ☐ | ☐ |
| 3. Repeats the same things over and over (questions, stories, or statements) | ☐ | ☐ | ☐ |
| 4. Trouble learning how to use a tool, appliance, or gadget (e.g., VCR, computer, microwave, remote control) | ☐ | ☐ | ☐ |
| 5. Forgets correct month or year | ☐ | ☐ | ☐ |
| 6. Trouble handling complicated financial affairs (e.g., balancing checkbook, income taxes, paying bills) | ☐ | ☐ | ☐ |
| 7. Trouble remembering appointments | ☐ | ☐ | ☐ |
| 8. Daily problems with thinking and/or memory | ☐ | ☐ | ☐ |
| | | Total Score [0-8] | ☐ |

CRU #044 TRIC VCI Plate #022 Screening

**Subject ID:** ☐☐ ☐☐☐ *Centre* *Subject ID*

**Date:** ☐☐☐☐ ☐☐ ☐☐ *yyyy* *mm* *dd*

# INFORMANT IQCODE *(page 1 of 2)*

Now we want you to remember what your friend or relative was like **10 years ago** and to compare it with what he/she is like **now**. Below are situations where this person has to use his/her memory or intelligence and we want you to indicate whether this has improved, stayed the same or got worse in that situation over the past 10 years. Please place an 'X' in the appropriate box.

Note the importance of comparing his/her present performance with 10 years ago. So if 10 years ago this person always forgot where he/she had left things, and he/she still does, then this would be considered "Hasn't changed much". Please indicate the changes you have observed by circling the appropriate answer.

| | Much improved | A bit improved | Not much change | A bit worse | Much worse |
|---|---|---|---|---|---|
| 1. Remembering things about family and friends e.g. occupations, birthdays, addresses | ☐ | ☐ | ☐ | ☐ | ☐ |
| 2. Remembering things that have happened recently | ☐ | ☐ | ☐ | ☐ | ☐ |
| 3. Recalling conversations a few days later | ☐ | ☐ | ☐ | ☐ | ☐ |
| 4. Remembering his/her address and telephone number | ☐ | ☐ | ☐ | ☐ | ☐ |
| 5. Remembering what day and month it is | ☐ | ☐ | ☐ | ☐ | ☐ |
| 6. Remembering where things are usually kept | ☐ | ☐ | ☐ | ☐ | ☐ |
| 7. Remembering where to find things which have been put in a different place from usual | ☐ | ☐ | ☐ | ☐ | ☐ |
| 8. Knowing how to work familiar machines around the house | ☐ | ☐ | ☐ | ☐ | ☐ |
| 9. Learning to use a new gadget or machine around the house | ☐ | ☐ | ☐ | ☐ | ☐ |
| 10. Learning new things in general | ☐ | ☐ | ☐ | ☐ | ☐ |
| 11. Following a story in a book or on TV | ☐ | ☐ | ☐ | ☐ | ☐ |
| 12. Making decisions on everyday matters | ☐ | ☐ | ☐ | ☐ | ☐ |

CRU #044 TRIC VCI Plate #023 Screening

**Subject ID:** ☐☐ ☐☐☐ (Centre / Subject ID)

**Date:** ☐☐☐☐ ☐☐ ☐☐ (yyyy / mm / dd)

## INFORMANT IQCODE *(page 2 of 2)*

| | Much improved | A bit improved | Not much change | A bit worse | Much worse |
|---|---|---|---|---|---|
| 13. Handling money for shopping | ☐ | ☐ | ☐ | ☐ | ☐ |
| 14. Handling financial matters e.g. the pension, dealing with the bank | ☐ | ☐ | ☐ | ☐ | ☐ |
| 15. Handling other everyday arithmetic problems e.g. knowing how much food to buy, knowing how long between visits from family or friends | ☐ | ☐ | ☐ | ☐ | ☐ |
| 16. Using his/her intelligence to understand what's going on and to reason things through | ☐ | ☐ | ☐ | ☐ | ☐ |

CRU #044 TRIC VCI Plate #024

☐ Randomization ☐ End
☐ Follow Up

**Subject ID:** ☐☐ ☐☐☐ (Centre / Subject ID) **Date:** ☐☐☐☐ ☐☐ ☐☐ (yyyy / mm / dd)

# INFORMANT MBI TRACKING TOOL *(page 1 of 3)*

Please score each item for its presence over the **last 2 weeks** (continuously or on and off). If present, items should reflect a **change** from the longstanding pattern of behavior. Otherwise, check "No".

Please rate severity: **1 = Mild** (noticeable, but of minor significance); **2 = Moderate** (significant, but not dramatic); **3 = Severe** (very marked or prominent, or dramatic change). If more than 1 item in a question, rate the most severe.

| | YES | NO | SEVERITY |
|---|---|---|---|
| ***This domain describes interest, motivation, and drive*** | | | |
| Uninterested in friends, family, or home activities. | ☐ | ☐ | ☐1 ☐2 ☐3 |
| Lacking curiosity in topics that would usually have attracted interest. | ☐ | ☐ | ☐1 ☐2 ☐3 |
| Being less spontaneous and active – for example, less likely to initiate or maintain conversation. | ☐ | ☐ | ☐1 ☐2 ☐3 |
| Unmotivated to act on obligations or interests. | ☐ | ☐ | ☐1 ☐2 ☐3 |
| Lacking in affection or emotions when compared to usual self. | ☐ | ☐ | ☐1 ☐2 ☐3 |
| No longer caring about anything. | ☐ | ☐ | ☐1 ☐2 ☐3 |
| ***This domain describes mood or anxiety symptoms*** | | | |
| Sadness or being in low spirits. Episodes of tearfulness. | ☐ | ☐ | ☐1 ☐2 ☐3 |
| Less able to experience pleasure. | ☐ | ☐ | ☐1 ☐2 ☐3 |
| Feeling discouraged about the future or feeling like a failure. | ☐ | ☐ | ☐1 ☐2 ☐3 |
| Viewing self as a burden to family and friends. | ☐ | ☐ | ☐1 ☐2 ☐3 |
| Being more anxious or worried about things that are routine (e.g. events, visits, etc.). | ☐ | ☐ | ☐1 ☐2 ☐3 |
| Feeling very tense, having an inability to relax, or having shakiness, or symptoms of panic. | ☐ | ☐ | ☐1 ☐2 ☐3 |

CRU #044 TRIC VCI Plate #025

☐ Randomization ☐ End
☐ Follow Up

**Subject ID:** ☐☐ ☐☐☐ (Centre / Subject ID) **Date:** ☐☐☐☐ ☐☐ ☐☐ (yyyy / mm / dd)

## INFORMANT MBI TRACKING TOOL *(page 2 of 3)*

| | YES | NO | SEVERITY |
|---|---|---|---|
| ***This domain describes the ability to delay gratification and control behavior, impulses, oral intake and/or changes in reward*** | | | |
| Agitation, aggression, irritability, or being temperamental. | ☐ | ☐ | ☐1 ☐2 ☐3 |
| Being unreasonably or uncharacteristically argumentative. | ☐ | ☐ | ☐1 ☐2 ☐3 |
| Impulsivity. Seeming to act without considering things. | ☐ | ☐ | ☐1 ☐2 ☐3 |
| Sexually disinhibited or intrusive behaviour, such as touching (self/others), hugging, groping, etc., in a manner that is out of character or may cause offence. | ☐ | ☐ | ☐1 ☐2 ☐3 |
| Frustration or impatience. Having troubles coping with delays, or waiting for events or for one's turn? | ☐ | ☐ | ☐1 ☐2 ☐3 |
| Recklessness or lack of judgement when driving (e.g. speeding, erratic swerving, abrupt lane changes, etc.). | ☐ | ☐ | ☐1 ☐2 ☐3 |
| Stubbornness or rigidity, i.e., uncharacteristically insistent on having one's own way, or being unwilling/unable to see/hear other views. | ☐ | ☐ | ☐1 ☐2 ☐3 |
| Change in eating behaviors (e.g., overeating, cramming the mouth, insistent on eating only specific foods, or eating the food in exactly the same order). | ☐ | ☐ | ☐1 ☐2 ☐3 |
| Not finding food tasteful or enjoyable. Eating less. | ☐ | ☐ | ☐1 ☐2 ☐3 |
| Hoarding objects. | ☐ | ☐ | ☐1 ☐2 ☐3 |
| Simple repetitive behaviors or compulsions. | ☐ | ☐ | ☐1 ☐2 ☐3 |
| Trouble regulating smoking, alcohol, drug intake, gambling, or shoplifting. | ☐ | ☐ | ☐1 ☐2 ☐3 |
| ***This domain describes following societal norms and having social graces, tact, and empathy*** | | | |
| Unconcerned about how one's words or actions affect others. Insensitivity to others' feelings. | ☐ | ☐ | ☐1 ☐2 ☐3 |
| Talking openly about very personal or private matters not usually discussed in public. | ☐ | ☐ | ☐1 ☐2 ☐3 |
| Saying rude or crude things or making lewd sexual remarks. | ☐ | ☐ | ☐1 ☐2 ☐3 |
| Lacking the social judgement about what to say or how to behave in public or private. | ☐ | ☐ | ☐1 ☐2 ☐3 |
| Talking to strangers as if familiar, or intruding on their activities. | ☐ | ☐ | ☐1 ☐2 ☐3 |

CRU #044 TRIC VCI Plate #026

☐ Randomization ☐ End
☐ Follow Up

**Subject ID:** ☐☐ ☐☐☐ (Centre / Subject ID)

**Date:** ☐☐☐☐ ☐☐ ☐☐ (yyyy / mm / dd)

# INFORMANT MBI TRACKING TOOL *(page 3 of 3)*

| | YES | NO | SEVERITY |
|---|---|---|---|
| ***This domain describes strongly held beliefs and sensory experiences*** | | | |
| Having beliefs that one is in danger, or that others are planning harm or to steal one's belongings. | ☐ | ☐ | ☐1 ☐2 ☐3 |
| Suspiciousness about the intentions or motives of other people. | ☐ | ☐ | ☐1 ☐2 ☐3 |
| Unrealistic beliefs about one's power, wealth or skills. | ☐ | ☐ | ☐1 ☐2 ☐3 |
| Hearing voices or talking to imaginary people or "spirits". | ☐ | ☐ | ☐1 ☐2 ☐3 |
| Seeing things (e.g. people, animals or insects) that are not there, i.e., that are imaginary to others? | ☐ | ☐ | ☐1 ☐2 ☐3 |

CRU #044 TRIC VCI Plate #027 Randomization

**Subject ID:** ☐☐ ☐☐☐ *Centre* *Subject ID*

**Date:** ☐☐☐☐ ☐☐ ☐☐ *yyyy* *mm* *dd*

# RUN-IN PATIENT DIARY - ONCE DAILY - WEEK 1

Date that the week started on: ☐☐☐☐ ☐☐ ☐☐ *yyyy* *mm* *dd*

| Day No. | Day of the week (Mon/Tue/ Wed/Thu/ Fri/Sat/Sun) | I finished the whole treatment | I started but did not finish | I missed the treatment | Blood Pressure (mmHg) | Pain (check the number that best represents the maximum pain you experience during the session, if any) |
|---|---|---|---|---|---|---|
| 1 | ___ | ☐ | ☐ | ☐ | ☐☐☐ / ☐☐ | ☐ 0 ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10 |
| 2 | ___ | ☐ | ☐ | ☐ | ☐☐☐ / ☐☐ | ☐ 0 ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10 |
| 3 | ___ | ☐ | ☐ | ☐ | ☐☐☐ / ☐☐ | ☐ 0 ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10 |
| 4 | ___ | ☐ | ☐ | ☐ | ☐☐☐ / ☐☐ | ☐ 0 ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10 |
| 5 | ___ | ☐ | ☐ | ☐ | ☐☐☐ / ☐☐ | ☐ 0 ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10 |
| 6 | ___ | ☐ | ☐ | ☐ | ☐☐☐ / ☐☐ | ☐ 0 ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10 |
| 7 | ___ | ☐ | ☐ | ☐ | ☐☐☐ / ☐☐ | ☐ 0 ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10 |

CRU #044 TRIC VCI Plate #028 Randomization

**Subject ID:** ☐☐ (Centre) ☐☐☐ (Subject ID) **Date:** ☐☐☐☐ (yyyy) ☐☐ (mm) ☐☐ (dd)

# RUN-IN PATIENT DIARY - ONCE DAILY - WEEK 2

Date that the week started on: ☐☐☐☐ (yyyy) ☐☐ (mm) ☐☐ (dd)

| Day No. | Day of the week (Mon/Tue/ Wed/Thu/ Fri/Sat/Sun) | I finished the whole treatment | I started but did not finish | I missed the treatment | Blood Pressure (mmHg) | Pain (check the number that best represents the maximum pain you experience during the session, if any) |
|---|---|---|---|---|---|---|
| 1 | ___ | ☐ | ☐ | ☐ | ☐☐☐ / ☐☐ | ☐ 0 ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10 |
| 2 | ___ | ☐ | ☐ | ☐ | ☐☐☐ / ☐☐ | ☐ 0 ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10 |
| 3 | ___ | ☐ | ☐ | ☐ | ☐☐☐ / ☐☐ | ☐ 0 ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10 |
| 4 | ___ | ☐ | ☐ | ☐ | ☐☐☐ / ☐☐ | ☐ 0 ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10 |
| 5 | ___ | ☐ | ☐ | ☐ | ☐☐☐ / ☐☐ | ☐ 0 ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10 |
| 6 | ___ | ☐ | ☐ | ☐ | ☐☐☐ / ☐☐ | ☐ 0 ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10 |
| 7 | ___ | ☐ | ☐ | ☐ | ☐☐☐ / ☐☐ | ☐ 0 ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10 |

CRU #044 TRIC VCI Plate #029 Randomization

**Subject ID:** ☐☐ ☐☐☐ *Centre* *Subject ID*

**Date:** ☐☐☐☐ ☐☐ ☐☐ *yyyy* *mm* *dd*

# RUN-IN PATIENT DIARY - ONCE DAILY - WEEK 3

Date that the week started on: ☐☐☐☐ ☐☐ ☐☐ *yyyy* *mm* *dd*

| Day No. | Day of the week (Mon/Tue/ Wed/Thu/ Fri/Sat/Sun) | I finished the whole treatment | I started but did not finish | I missed the treatment | Blood Pressure (mmHg) | Pain (check the number that best represents the maximum pain you experience during the session, if any) |
|---|---|---|---|---|---|---|
| 1 | ___ | ☐ | ☐ | ☐ | ☐☐☐ / ☐☐ | ☐0 ☐1 ☐2 ☐3 ☐4 ☐5 ☐6 ☐7 ☐8 ☐9 ☐10 |
| 2 | ___ | ☐ | ☐ | ☐ | ☐☐☐ / ☐☐ | ☐0 ☐1 ☐2 ☐3 ☐4 ☐5 ☐6 ☐7 ☐8 ☐9 ☐10 |
| 3 | ___ | ☐ | ☐ | ☐ | ☐☐☐ / ☐☐ | ☐0 ☐1 ☐2 ☐3 ☐4 ☐5 ☐6 ☐7 ☐8 ☐9 ☐10 |
| 4 | ___ | ☐ | ☐ | ☐ | ☐☐☐ / ☐☐ | ☐0 ☐1 ☐2 ☐3 ☐4 ☐5 ☐6 ☐7 ☐8 ☐9 ☐10 |
| 5 | ___ | ☐ | ☐ | ☐ | ☐☐☐ / ☐☐ | ☐0 ☐1 ☐2 ☐3 ☐4 ☐5 ☐6 ☐7 ☐8 ☐9 ☐10 |
| 6 | ___ | ☐ | ☐ | ☐ | ☐☐☐ / ☐☐ | ☐0 ☐1 ☐2 ☐3 ☐4 ☐5 ☐6 ☐7 ☐8 ☐9 ☐10 |
| 7 | ___ | ☐ | ☐ | ☐ | ☐☐☐ / ☐☐ | ☐0 ☐1 ☐2 ☐3 ☐4 ☐5 ☐6 ☐7 ☐8 ☐9 ☐10 |

CRU #044 TRIC VCI Plate #030 Follow Up

**Subject ID:** Centre Subject ID **Date:** yyyy mm dd

# PATIENT DIARY - ONCE DAILY - WEEK 1

Date that the week started on: yyyy mm dd

| Day No. | Day of the week (Mon/Tue/ Wed/Thu/ Fri/Sat/Sun) | I finished the whole treatment | I started but did not finish | I missed the treatment | Blood Pressure (mmHg) | Pain (check the number that best represents the maximum pain you experience during the session, if any) |
|---|---|---|---|---|---|---|
| 1 | ___ | ☐ | ☐ | ☐ | ☐☐☐ / ☐☐ | ☐0 ☐1 ☐2 ☐3 ☐4 ☐5 ☐6 ☐7 ☐8 ☐9 ☐10 |
| 2 | ___ | ☐ | ☐ | ☐ | ☐☐☐ / ☐☐ | ☐0 ☐1 ☐2 ☐3 ☐4 ☐5 ☐6 ☐7 ☐8 ☐9 ☐10 |
| 3 | ___ | ☐ | ☐ | ☐ | ☐☐☐ / ☐☐ | ☐0 ☐1 ☐2 ☐3 ☐4 ☐5 ☐6 ☐7 ☐8 ☐9 ☐10 |
| 4 | ___ | ☐ | ☐ | ☐ | ☐☐☐ / ☐☐ | ☐0 ☐1 ☐2 ☐3 ☐4 ☐5 ☐6 ☐7 ☐8 ☐9 ☐10 |
| 5 | ___ | ☐ | ☐ | ☐ | ☐☐☐ / ☐☐ | ☐0 ☐1 ☐2 ☐3 ☐4 ☐5 ☐6 ☐7 ☐8 ☐9 ☐10 |
| 6 | ___ | ☐ | ☐ | ☐ | ☐☐☐ / ☐☐ | ☐0 ☐1 ☐2 ☐3 ☐4 ☐5 ☐6 ☐7 ☐8 ☐9 ☐10 |
| 7 | ___ | ☐ | ☐ | ☐ | ☐☐☐ / ☐☐ | ☐0 ☐1 ☐2 ☐3 ☐4 ☐5 ☐6 ☐7 ☐8 ☐9 ☐10 |

CRU #044 TRIC VCI  Plate #031  Follow Up

**Subject ID:** ☐☐ ☐☐☐ (*Centre* / *Subject ID*)  **Date:** ☐☐☐☐ ☐☐ ☐☐ (*yyyy* / *mm* / *dd*)

# PATIENT DIARY - ONCE DAILY - WEEK 2

Date that the week started on: ☐☐☐☐ ☐☐ ☐☐ (*yyyy* / *mm* / *dd*)

| Day No. | Day of the week (Mon/Tue/ Wed/Thu/ Fri/Sat/Sun) | I finished the whole treatment | I started but did not finish | I missed the treatment | Blood Pressure (mmHg) | Pain (check the number that best represents the maximum pain you experience during the session, if any) |
|---|---|---|---|---|---|---|
| 1 | ___ | ☐ | ☐ | ☐ | ☐☐☐/☐☐ | ☐0 ☐1 ☐2 ☐3 ☐4 ☐5 ☐6 ☐7 ☐8 ☐9 ☐10 |
| 2 | ___ | ☐ | ☐ | ☐ | ☐☐☐/☐☐ | ☐0 ☐1 ☐2 ☐3 ☐4 ☐5 ☐6 ☐7 ☐8 ☐9 ☐10 |
| 3 | ___ | ☐ | ☐ | ☐ | ☐☐☐/☐☐ | ☐0 ☐1 ☐2 ☐3 ☐4 ☐5 ☐6 ☐7 ☐8 ☐9 ☐10 |
| 4 | ___ | ☐ | ☐ | ☐ | ☐☐☐/☐☐ | ☐0 ☐1 ☐2 ☐3 ☐4 ☐5 ☐6 ☐7 ☐8 ☐9 ☐10 |
| 5 | ___ | ☐ | ☐ | ☐ | ☐☐☐/☐☐ | ☐0 ☐1 ☐2 ☐3 ☐4 ☐5 ☐6 ☐7 ☐8 ☐9 ☐10 |
| 6 | ___ | ☐ | ☐ | ☐ | ☐☐☐/☐☐ | ☐0 ☐1 ☐2 ☐3 ☐4 ☐5 ☐6 ☐7 ☐8 ☐9 ☐10 |
| 7 | ___ | ☐ | ☐ | ☐ | ☐☐☐/☐☐ | ☐0 ☐1 ☐2 ☐3 ☐4 ☐5 ☐6 ☐7 ☐8 ☐9 ☐10 |

CRU #044 TRIC VCI Plate #032 Follow Up

**Subject ID:** ☐☐ ☐☐☐ *Centre* *Subject ID*

**Date:** ☐☐☐☐ ☐☐ ☐☐ *yyyy* *mm* *dd*

# PATIENT DIARY - ONCE DAILY - WEEK 3

Date that the week started on: ☐☐☐☐ ☐☐ ☐☐ *yyyy* *mm* *dd*

| Day No. | Day of the week (Mon/Tue/ Wed/Thu/ Fri/Sat/Sun) | I finished the whole treatment | I started but did not finish | I missed the treatment | Blood Pressure (mmHg) | Pain (check the number that best represents the maximum pain you experience during the session, if any) |
|---|---|---|---|---|---|---|
| 1 | ___ | ☐ | ☐ | ☐ | ☐☐☐ / ☐☐ | ☐0 ☐1 ☐2 ☐3 ☐4 ☐5 ☐6 ☐7 ☐8 ☐9 ☐10 |
| 2 | ___ | ☐ | ☐ | ☐ | ☐☐☐ / ☐☐ | ☐0 ☐1 ☐2 ☐3 ☐4 ☐5 ☐6 ☐7 ☐8 ☐9 ☐10 |
| 3 | ___ | ☐ | ☐ | ☐ | ☐☐☐ / ☐☐ | ☐0 ☐1 ☐2 ☐3 ☐4 ☐5 ☐6 ☐7 ☐8 ☐9 ☐10 |
| 4 | ___ | ☐ | ☐ | ☐ | ☐☐☐ / ☐☐ | ☐0 ☐1 ☐2 ☐3 ☐4 ☐5 ☐6 ☐7 ☐8 ☐9 ☐10 |
| 5 | ___ | ☐ | ☐ | ☐ | ☐☐☐ / ☐☐ | ☐0 ☐1 ☐2 ☐3 ☐4 ☐5 ☐6 ☐7 ☐8 ☐9 ☐10 |
| 6 | ___ | ☐ | ☐ | ☐ | ☐☐☐ / ☐☐ | ☐0 ☐1 ☐2 ☐3 ☐4 ☐5 ☐6 ☐7 ☐8 ☐9 ☐10 |
| 7 | ___ | ☐ | ☐ | ☐ | ☐☐☐ / ☐☐ | ☐0 ☐1 ☐2 ☐3 ☐4 ☐5 ☐6 ☐7 ☐8 ☐9 ☐10 |

CRU #044 TRIC VCI Plate #033 Follow Up

**Subject ID:** ☐☐ ☐☐☐ *Centre* *Subject ID*

**Date:** ☐☐☐☐ ☐☐ ☐☐ *yyyy* *mm* *dd*

# PATIENT DIARY - ONCE DAILY - WEEK 4

Date that the week started on: ☐☐☐☐ ☐☐ ☐☐ *yyyy* *mm* *dd*

| Day No. | Day of the week (Mon/Tue/ Wed/Thu/ Fri/Sat/Sun) | I finished the whole treatment | I started but did not finish | I missed the treatment | Blood Pressure (mmHg) | Pain (check the number that best represents the maximum pain you experience during the session, if any) |
|---|---|---|---|---|---|---|
| 1 | ___ | ☐ | ☐ | ☐ | ☐☐☐ / ☐☐ | ☐ 0 ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10 |
| 2 | ___ | ☐ | ☐ | ☐ | ☐☐☐ / ☐☐ | ☐ 0 ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10 |
| 3 | ___ | ☐ | ☐ | ☐ | ☐☐☐ / ☐☐ | ☐ 0 ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10 |
| 4 | ___ | ☐ | ☐ | ☐ | ☐☐☐ / ☐☐ | ☐ 0 ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10 |
| 5 | ___ | ☐ | ☐ | ☐ | ☐☐☐ / ☐☐ | ☐ 0 ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10 |
| 6 | ___ | ☐ | ☐ | ☐ | ☐☐☐ / ☐☐ | ☐ 0 ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10 |
| 7 | ___ | ☐ | ☐ | ☐ | ☐☐☐ / ☐☐ | ☐ 0 ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10 |

CRU #044 TRIC VCI Plate #034 Follow Up

**Subject ID:** ☐☐ ☐☐☐ *Centre* *Subject ID*

**Date:** ☐☐☐☐ ☐☐ ☐☐ *yyyy* *mm* *dd*

# PATIENT DIARY - ONCE DAILY - WEEK 5

Date that the week started on: ☐☐☐☐ ☐☐ ☐☐ *yyyy* *mm* *dd*

| Day No. | Day of the week (Mon/Tue/ Wed/Thu/ Fri/Sat/Sun) | I finished the whole treatment | I started but did not finish | I missed the treatment | Blood Pressure (mmHg) | Pain (check the number that best represents the maximum pain you experience during the session, if any) |
|---|---|---|---|---|---|---|
| 1 | ___ | ☐ | ☐ | ☐ | ☐☐☐ / ☐☐ | ☐0 ☐1 ☐2 ☐3 ☐4 ☐5 ☐6 ☐7 ☐8 ☐9 ☐10 |
| 2 | ___ | ☐ | ☐ | ☐ | ☐☐☐ / ☐☐ | ☐0 ☐1 ☐2 ☐3 ☐4 ☐5 ☐6 ☐7 ☐8 ☐9 ☐10 |
| 3 | ___ | ☐ | ☐ | ☐ | ☐☐☐ / ☐☐ | ☐0 ☐1 ☐2 ☐3 ☐4 ☐5 ☐6 ☐7 ☐8 ☐9 ☐10 |
| 4 | ___ | ☐ | ☐ | ☐ | ☐☐☐ / ☐☐ | ☐0 ☐1 ☐2 ☐3 ☐4 ☐5 ☐6 ☐7 ☐8 ☐9 ☐10 |
| 5 | ___ | ☐ | ☐ | ☐ | ☐☐☐ / ☐☐ | ☐0 ☐1 ☐2 ☐3 ☐4 ☐5 ☐6 ☐7 ☐8 ☐9 ☐10 |
| 6 | ___ | ☐ | ☐ | ☐ | ☐☐☐ / ☐☐ | ☐0 ☐1 ☐2 ☐3 ☐4 ☐5 ☐6 ☐7 ☐8 ☐9 ☐10 |
| 7 | ___ | ☐ | ☐ | ☐ | ☐☐☐ / ☐☐ | ☐0 ☐1 ☐2 ☐3 ☐4 ☐5 ☐6 ☐7 ☐8 ☐9 ☐10 |

CRU #044 TRIC VCI Plate #035 Follow Up

**Subject ID:** ☐☐ ☐☐☐ *Centre* *Subject ID*

**Date:** ☐☐☐☐ ☐☐ ☐☐ *yyyy* *mm* *dd*

# PATIENT DIARY - TWICE DAILY - WEEK 1 *(page 1 of 2)*

Date that the week started on: ☐☐☐☐ ☐☐ ☐☐ *yyyy* *mm* *dd*

| Day No. | Day of the week (Mon/Tue/Wed/Thu/Fri/Sat/Sun) | Time | I finished the whole treatment | I started but did not finish | I missed the treament | Blood Pressure (mmHg) | Pain (check the number that best represents the maximum pain you experience during the session, if any) |
|---|---|---|---|---|---|---|---|
| 1 | — — — | AM | ☐ | ☐ | ☐ | ☐☐☐ / ☐☐ | ☐0 ☐1 ☐2 ☐3 ☐4 ☐5 ☐6 ☐7 ☐8 ☐9 ☐10 |
| | | PM | ☐ | ☐ | ☐ | ☐☐☐ / ☐☐ | ☐0 ☐1 ☐2 ☐3 ☐4 ☐5 ☐6 ☐7 ☐8 ☐9 ☐10 |
| 2 | | AM | ☐ | ☐ | ☐ | ☐☐☐ / ☐☐ | ☐0 ☐1 ☐2 ☐3 ☐4 ☐5 ☐6 ☐7 ☐8 ☐9 ☐10 |
| | | PM | ☐ | ☐ | ☐ | ☐☐☐ / ☐☐ | ☐0 ☐1 ☐2 ☐3 ☐4 ☐5 ☐6 ☐7 ☐8 ☐9 ☐10 |
| 3 | | AM | ☐ | ☐ | ☐ | ☐☐☐ / ☐☐ | ☐0 ☐1 ☐2 ☐3 ☐4 ☐5 ☐6 ☐7 ☐8 ☐9 ☐10 |
| | | PM | ☐ | ☐ | ☐ | ☐☐☐ / ☐☐ | ☐0 ☐1 ☐2 ☐3 ☐4 ☐5 ☐6 ☐7 ☐8 ☐9 ☐10 |

CRU #044 TRIC VCI Plate #036 Follow Up

**Subject ID:** Centre Subject ID **Date:** yyyy mm dd

# PATIENT DIARY - TWICE DAILY - WEEK 1 *(page 2 of 2)*

| Day No. | Day of the week (Mon/Tue/Wed/Thu/Fri/Sat/Sun) | Time | I finished the whole treatment | I started but did not finish | I missed the treament | Blood Pressure (mmHg) | Pain (check the number that best represents the maximum pain you experience during the session, if any) |
|---|---|---|---|---|---|---|---|
| 4 | ___ | AM | ☐ | ☐ | ☐ | ☐☐☐ / ☐☐ | ☐0 ☐1 ☐2 ☐3 ☐4 ☐5 ☐6 ☐7 ☐8 ☐9 ☐10 |
| | | PM | ☐ | ☐ | ☐ | ☐☐☐ / ☐☐ | ☐0 ☐1 ☐2 ☐3 ☐4 ☐5 ☐6 ☐7 ☐8 ☐9 ☐10 |
| 5 | ___ | AM | ☐ | ☐ | ☐ | ☐☐☐ / ☐☐ | ☐0 ☐1 ☐2 ☐3 ☐4 ☐5 ☐6 ☐7 ☐8 ☐9 ☐10 |
| | | PM | ☐ | ☐ | ☐ | ☐☐☐ / ☐☐ | ☐0 ☐1 ☐2 ☐3 ☐4 ☐5 ☐6 ☐7 ☐8 ☐9 ☐10 |
| 6 | ___ | AM | ☐ | ☐ | ☐ | ☐☐☐ / ☐☐ | ☐0 ☐1 ☐2 ☐3 ☐4 ☐5 ☐6 ☐7 ☐8 ☐9 ☐10 |
| | | PM | ☐ | ☐ | ☐ | ☐☐☐ / ☐☐ | ☐0 ☐1 ☐2 ☐3 ☐4 ☐5 ☐6 ☐7 ☐8 ☐9 ☐10 |
| 7 | ___ | AM | ☐ | ☐ | ☐ | ☐☐☐ / ☐☐ | ☐0 ☐1 ☐2 ☐3 ☐4 ☐5 ☐6 ☐7 ☐8 ☐9 ☐10 |
| | | PM | ☐ | ☐ | ☐ | ☐☐☐ / ☐☐ | ☐0 ☐1 ☐2 ☐3 ☐4 ☐5 ☐6 ☐7 ☐8 ☐9 ☐10 |

CRU #044 TRIC VCI Plate #037 Follow Up

**Subject ID:** ☐☐ ☐☐☐ (Centre / Subject ID)

**Date:** ☐☐☐☐ ☐☐ ☐☐ (yyyy / mm / dd)

# PATIENT DIARY - TWICE DAILY - WEEK 2 *(page 1 of 2)*

Date that the week started on: ☐☐☐☐ ☐☐ ☐☐ (yyyy / mm / dd)

| Day No. | Day of the week (Mon/Tue/Wed/Thu/Fri/Sat/Sun) | Time | I finished the whole treatment | I started but did not finish | I missed the treament | Blood Pressure (mmHg) | Pain (check the number that best represents the maximum pain you experience during the session, if any) |
|---|---|---|---|---|---|---|---|
| 1 | — — — | AM | ☐ | ☐ | ☐ | ☐☐☐ / ☐☐ | ☐0 ☐1 ☐2 ☐3 ☐4 ☐5 ☐6 ☐7 ☐8 ☐9 ☐10 |
| | | PM | ☐ | ☐ | ☐ | ☐☐☐ / ☐☐ | ☐0 ☐1 ☐2 ☐3 ☐4 ☐5 ☐6 ☐7 ☐8 ☐9 ☐10 |
| 2 | | AM | ☐ | ☐ | ☐ | ☐☐☐ / ☐☐ | ☐0 ☐1 ☐2 ☐3 ☐4 ☐5 ☐6 ☐7 ☐8 ☐9 ☐10 |
| | | PM | ☐ | ☐ | ☐ | ☐☐☐ / ☐☐ | ☐0 ☐1 ☐2 ☐3 ☐4 ☐5 ☐6 ☐7 ☐8 ☐9 ☐10 |
| 3 | | AM | ☐ | ☐ | ☐ | ☐☐☐ / ☐☐ | ☐0 ☐1 ☐2 ☐3 ☐4 ☐5 ☐6 ☐7 ☐8 ☐9 ☐10 |
| | | PM | ☐ | ☐ | ☐ | ☐☐☐ / ☐☐ | ☐0 ☐1 ☐2 ☐3 ☐4 ☐5 ☐6 ☐7 ☐8 ☐9 ☐10 |

CRU #044 TRIC VCI Plate #038 Follow Up

**Subject ID:** ☐☐ ☐☐☐ *Centre* *Subject ID*

**Date:** ☐☐☐☐ ☐☐ ☐☐ *yyyy* *mm* *dd*

# PATIENT DIARY - TWICE DAILY - WEEK 2 *(page 2 of 2)*

| Day No. | Day of the week (Mon/Tue/Wed/Thu/Fri/Sat/Sun) | Time | I finished the whole treatment | I started but did not finish | I missed the treament | Blood Pressure (mmHg) | Pain (check the number that best represents the maximum pain you experience during the session, if any) |
|---|---|---|---|---|---|---|---|
| 4 | ___ | AM | ☐ | ☐ | ☐ | ☐☐☐ / ☐☐ | ☐0 ☐1 ☐2 ☐3 ☐4 ☐5 ☐6 ☐7 ☐8 ☐9 ☐10 |
| | | PM | ☐ | ☐ | ☐ | ☐☐☐ / ☐☐ | ☐0 ☐1 ☐2 ☐3 ☐4 ☐5 ☐6 ☐7 ☐8 ☐9 ☐10 |
| 5 | ___ | AM | ☐ | ☐ | ☐ | ☐☐☐ / ☐☐ | ☐0 ☐1 ☐2 ☐3 ☐4 ☐5 ☐6 ☐7 ☐8 ☐9 ☐10 |
| | | PM | ☐ | ☐ | ☐ | ☐☐☐ / ☐☐ | ☐0 ☐1 ☐2 ☐3 ☐4 ☐5 ☐6 ☐7 ☐8 ☐9 ☐10 |
| 6 | ___ | AM | ☐ | ☐ | ☐ | ☐☐☐ / ☐☐ | ☐0 ☐1 ☐2 ☐3 ☐4 ☐5 ☐6 ☐7 ☐8 ☐9 ☐10 |
| | | PM | ☐ | ☐ | ☐ | ☐☐☐ / ☐☐ | ☐0 ☐1 ☐2 ☐3 ☐4 ☐5 ☐6 ☐7 ☐8 ☐9 ☐10 |
| 7 | ___ | AM | ☐ | ☐ | ☐ | ☐☐☐ / ☐☐ | ☐0 ☐1 ☐2 ☐3 ☐4 ☐5 ☐6 ☐7 ☐8 ☐9 ☐10 |
| | | PM | ☐ | ☐ | ☐ | ☐☐☐ / ☐☐ | ☐0 ☐1 ☐2 ☐3 ☐4 ☐5 ☐6 ☐7 ☐8 ☐9 ☐10 |

CRU #044 TRIC VCI Plate #039 Follow Up

**Subject ID:** ☐☐ ☐☐☐ *Centre* *Subject ID*

**Date:** ☐☐☐☐ ☐☐ ☐☐ *yyyy* *mm* *dd*

# PATIENT DIARY - TWICE DAILY - WEEK 3 *(page 1 of 2)*

Date that the week started on: ☐☐☐☐ ☐☐ ☐☐ *yyyy* *mm* *dd*

| Day No. | Day of the week (Mon/Tue/Wed/Thu/Fri/Sat/Sun) | Time | I finished the whole treatment | I started but did not finish | I missed the treament | Blood Pressure (mmHg) | Pain (check the number that best represents the maximum pain you experience during the session, if any) |
|---|---|---|---|---|---|---|---|
| 1 | — — — | AM | ☐ | ☐ | ☐ | ☐☐☐ / ☐☐ | ☐0 ☐1 ☐2 ☐3 ☐4 ☐5 ☐6 ☐7 ☐8 ☐9 ☐10 |
| | | PM | ☐ | ☐ | ☐ | ☐☐☐ / ☐☐ | ☐0 ☐1 ☐2 ☐3 ☐4 ☐5 ☐6 ☐7 ☐8 ☐9 ☐10 |
| 2 | | AM | ☐ | ☐ | ☐ | ☐☐☐ / ☐☐ | ☐0 ☐1 ☐2 ☐3 ☐4 ☐5 ☐6 ☐7 ☐8 ☐9 ☐10 |
| | | PM | ☐ | ☐ | ☐ | ☐☐☐ / ☐☐ | ☐0 ☐1 ☐2 ☐3 ☐4 ☐5 ☐6 ☐7 ☐8 ☐9 ☐10 |
| 3 | | AM | ☐ | ☐ | ☐ | ☐☐☐ / ☐☐ | ☐0 ☐1 ☐2 ☐3 ☐4 ☐5 ☐6 ☐7 ☐8 ☐9 ☐10 |
| | | PM | ☐ | ☐ | ☐ | ☐☐☐ / ☐☐ | ☐0 ☐1 ☐2 ☐3 ☐4 ☐5 ☐6 ☐7 ☐8 ☐9 ☐10 |

CRU #044 TRIC VCI Plate #040 Follow Up

**Subject ID:** Centre Subject ID **Date:** yyyy mm dd

# PATIENT DIARY - TWICE DAILY - WEEK 3 *(page 2 of 2)*

| Day No. | Day of the week (Mon/Tue/Wed/Thu/Fri/Sat/Sun) | Time | I finished the whole treatment | I started but did not finish | I missed the treament | Blood Pressure (mmHg) | Pain (check the number that best represents the maximum pain you experience during the session, if any) |
|---|---|---|---|---|---|---|---|
| 4 | ___ | AM | ☐ | ☐ | ☐ | ☐☐☐ / ☐☐ | ☐0 ☐1 ☐2 ☐3 ☐4 ☐5 ☐6 ☐7 ☐8 ☐9 ☐10 |
| | | PM | ☐ | ☐ | ☐ | ☐☐☐ / ☐☐ | ☐0 ☐1 ☐2 ☐3 ☐4 ☐5 ☐6 ☐7 ☐8 ☐9 ☐10 |
| 5 | ___ | AM | ☐ | ☐ | ☐ | ☐☐☐ / ☐☐ | ☐0 ☐1 ☐2 ☐3 ☐4 ☐5 ☐6 ☐7 ☐8 ☐9 ☐10 |
| | | PM | ☐ | ☐ | ☐ | ☐☐☐ / ☐☐ | ☐0 ☐1 ☐2 ☐3 ☐4 ☐5 ☐6 ☐7 ☐8 ☐9 ☐10 |
| 6 | ___ | AM | ☐ | ☐ | ☐ | ☐☐☐ / ☐☐ | ☐0 ☐1 ☐2 ☐3 ☐4 ☐5 ☐6 ☐7 ☐8 ☐9 ☐10 |
| | | PM | ☐ | ☐ | ☐ | ☐☐☐ / ☐☐ | ☐0 ☐1 ☐2 ☐3 ☐4 ☐5 ☐6 ☐7 ☐8 ☐9 ☐10 |
| 7 | ___ | AM | ☐ | ☐ | ☐ | ☐☐☐ / ☐☐ | ☐0 ☐1 ☐2 ☐3 ☐4 ☐5 ☐6 ☐7 ☐8 ☐9 ☐10 |
| | | PM | ☐ | ☐ | ☐ | ☐☐☐ / ☐☐ | ☐0 ☐1 ☐2 ☐3 ☐4 ☐5 ☐6 ☐7 ☐8 ☐9 ☐10 |

CRU #044 TRIC VCI Plate #041 Follow Up

**Subject ID:** ☐☐ ☐☐☐ *Centre* *Subject ID*

**Date:** ☐☐☐☐ ☐☐ ☐☐ *yyyy* *mm* *dd*

# PATIENT DIARY - TWICE DAILY - WEEK 4 *(page 1 of 2)*

Date that the week started on: ☐☐☐☐ ☐☐ ☐☐ *yyyy* *mm* *dd*

| Day No. | Day of the week (Mon/Tue/Wed/Thu/Fri/Sat/Sun) | Time | I took the whole treatment | I started but did not finish | I missed the treament | Blood Pressure (mmHg) | Pain (check the number that best represents the maximum pain you experience during the session, if any) |
|---|---|---|---|---|---|---|---|
| 1 | — — — | AM | ☐ | ☐ | ☐ | ☐☐☐ / ☐☐ | ☐0 ☐1 ☐2 ☐3 ☐4 ☐5 ☐6 ☐7 ☐8 ☐9 ☐10 |
| | | PM | ☐ | ☐ | ☐ | ☐☐☐ / ☐☐ | ☐0 ☐1 ☐2 ☐3 ☐4 ☐5 ☐6 ☐7 ☐8 ☐9 ☐10 |
| 2 | | AM | ☐ | ☐ | ☐ | ☐☐☐ / ☐☐ | ☐0 ☐1 ☐2 ☐3 ☐4 ☐5 ☐6 ☐7 ☐8 ☐9 ☐10 |
| | | PM | ☐ | ☐ | ☐ | ☐☐☐ / ☐☐ | ☐0 ☐1 ☐2 ☐3 ☐4 ☐5 ☐6 ☐7 ☐8 ☐9 ☐10 |
| 3 | | AM | ☐ | ☐ | ☐ | ☐☐☐ / ☐☐ | ☐0 ☐1 ☐2 ☐3 ☐4 ☐5 ☐6 ☐7 ☐8 ☐9 ☐10 |
| | | PM | ☐ | ☐ | ☐ | ☐☐☐ / ☐☐ | ☐0 ☐1 ☐2 ☐3 ☐4 ☐5 ☐6 ☐7 ☐8 ☐9 ☐10 |

CRU #044 TRIC VCI Plate #042 Follow Up

**Subject ID:** ☐☐ ☐☐☐ *Centre* *Subject ID*

**Date:** ☐☐☐☐ ☐☐ ☐☐ *yyyy* *mm* *dd*

# PATIENT DIARY - TWICE DAILY - WEEK 4 *(page 2 of 2)*

| Day No. | Day of the week (Mon/Tue/Wed/Thu/Fri/Sat/Sun) | Time | I took the whole treatment | I started but did not complete | I missed the treament | Blood Pressure (mmHg) | Pain (check the number that best represents the maximum pain you experience during the session, if any) |
|---|---|---|---|---|---|---|---|
| 4 | ___ | AM | ☐ | ☐ | ☐ | ☐☐☐ / ☐☐ | ☐0 ☐1 ☐2 ☐3 ☐4 ☐5 ☐6 ☐7 ☐8 ☐9 ☐10 |
| | | PM | ☐ | ☐ | ☐ | ☐☐☐ / ☐☐ | ☐0 ☐1 ☐2 ☐3 ☐4 ☐5 ☐6 ☐7 ☐8 ☐9 ☐10 |
| 5 | ___ | AM | ☐ | ☐ | ☐ | ☐☐☐ / ☐☐ | ☐0 ☐1 ☐2 ☐3 ☐4 ☐5 ☐6 ☐7 ☐8 ☐9 ☐10 |
| | | PM | ☐ | ☐ | ☐ | ☐☐☐ / ☐☐ | ☐0 ☐1 ☐2 ☐3 ☐4 ☐5 ☐6 ☐7 ☐8 ☐9 ☐10 |
| 6 | ___ | AM | ☐ | ☐ | ☐ | ☐☐☐ / ☐☐ | ☐0 ☐1 ☐2 ☐3 ☐4 ☐5 ☐6 ☐7 ☐8 ☐9 ☐10 |
| | | PM | ☐ | ☐ | ☐ | ☐☐☐ / ☐☐ | ☐0 ☐1 ☐2 ☐3 ☐4 ☐5 ☐6 ☐7 ☐8 ☐9 ☐10 |
| 7 | ___ | AM | ☐ | ☐ | ☐ | ☐☐☐ / ☐☐ | ☐0 ☐1 ☐2 ☐3 ☐4 ☐5 ☐6 ☐7 ☐8 ☐9 ☐10 |
| | | PM | ☐ | ☐ | ☐ | ☐☐☐ / ☐☐ | ☐0 ☐1 ☐2 ☐3 ☐4 ☐5 ☐6 ☐7 ☐8 ☐9 ☐10 |

CRU #044 TRIC VCI Plate #043 Follow Up

**Subject ID:** Centre Subject ID **Date:** yyyy mm dd

# PATIENT DIARY - TWICE DAILY - WEEK 5 *(page 1 of 2)*

Date that the week started on: yyyy mm dd

| Day No. | Day of the week (Mon/Tue/Wed/Thu/Fri/Sat/Sun) | Time | I did the whole treatment | I started but did not | I missed the treament | Blood Pressure (mmHg) | Pain (check the number that best represents the maximum pain you experience during the session, if any) |
|---|---|---|---|---|---|---|---|
| 1 | — — — | AM | ☐ | ☐ | ☐ | ☐☐☐ / ☐☐ | ☐0 ☐1 ☐2 ☐3 ☐4 ☐5 ☐6 ☐7 ☐8 ☐9 ☐10 |
| | | PM | ☐ | ☐ | ☐ | ☐☐☐ / ☐☐ | ☐0 ☐1 ☐2 ☐3 ☐4 ☐5 ☐6 ☐7 ☐8 ☐9 ☐10 |
| 2 | | AM | ☐ | ☐ | ☐ | ☐☐☐ / ☐☐ | ☐0 ☐1 ☐2 ☐3 ☐4 ☐5 ☐6 ☐7 ☐8 ☐9 ☐10 |
| | | PM | ☐ | ☐ | ☐ | ☐☐☐ / ☐☐ | ☐0 ☐1 ☐2 ☐3 ☐4 ☐5 ☐6 ☐7 ☐8 ☐9 ☐10 |
| 3 | | AM | ☐ | ☐ | ☐ | ☐☐☐ / ☐☐ | ☐0 ☐1 ☐2 ☐3 ☐4 ☐5 ☐6 ☐7 ☐8 ☐9 ☐10 |
| | | PM | ☐ | ☐ | ☐ | ☐☐☐ / ☐☐ | ☐0 ☐1 ☐2 ☐3 ☐4 ☐5 ☐6 ☐7 ☐8 ☐9 ☐10 |

CRU #044 TRIC VCI Plate #044 Follow Up

**Subject ID:** ☐☐ ☐☐☐ *Centre* *Subject ID*

**Date:** ☐☐☐☐ ☐☐ ☐☐ *yyyy* *mm* *dd*

# PATIENT DIARY - TWICE DAILY - WEEK 5 *(page 2 of 2)*

| Day No. | Day of the week (Mon/Tue/ Wed/Thu/Fri/ Sat/Sun) | Time | I took the whole treatment | I started but did not finish | I missed the treament | Blood Pressure (mmHg) | Pain (check the number that best represents the maximum pain you experience during the session, if any) |
|---|---|---|---|---|---|---|---|
| 4 | ___ | AM | ☐ | ☐ | ☐ | ☐☐☐ / ☐☐ | ☐0 ☐1 ☐2 ☐3 ☐4 ☐5 ☐6 ☐7 ☐8 ☐9 ☐10 |
| | | PM | ☐ | ☐ | ☐ | ☐☐☐ / ☐☐ | ☐0 ☐1 ☐2 ☐3 ☐4 ☐5 ☐6 ☐7 ☐8 ☐9 ☐10 |
| 5 | ___ | AM | ☐ | ☐ | ☐ | ☐☐☐ / ☐☐ | ☐0 ☐1 ☐2 ☐3 ☐4 ☐5 ☐6 ☐7 ☐8 ☐9 ☐10 |
| | | PM | ☐ | ☐ | ☐ | ☐☐☐ / ☐☐ | ☐0 ☐1 ☐2 ☐3 ☐4 ☐5 ☐6 ☐7 ☐8 ☐9 ☐10 |
| 6 | ___ | AM | ☐ | ☐ | ☐ | ☐☐☐ / ☐☐ | ☐0 ☐1 ☐2 ☐3 ☐4 ☐5 ☐6 ☐7 ☐8 ☐9 ☐10 |
| | | PM | ☐ | ☐ | ☐ | ☐☐☐ / ☐☐ | ☐0 ☐1 ☐2 ☐3 ☐4 ☐5 ☐6 ☐7 ☐8 ☐9 ☐10 |
| 7 | ___ | AM | ☐ | ☐ | ☐ | ☐☐☐ / ☐☐ | ☐0 ☐1 ☐2 ☐3 ☐4 ☐5 ☐6 ☐7 ☐8 ☐9 ☐10 |
| | | PM | ☐ | ☐ | ☐ | ☐☐☐ / ☐☐ | ☐0 ☐1 ☐2 ☐3 ☐4 ☐5 ☐6 ☐7 ☐8 ☐9 ☐10 |

CRU #044 TRIC VCI Plate #045 Randomization

**Subject ID:** ☐☐ ☐☐☐ (Centre / Subject ID) **Date:** ☐☐☐☐ ☐☐ ☐☐ (yyyy / mm / dd)

## RANDOMIZATION

| | | |
|---|---|---|
| Was informed consent obtained? | ☐ Yes | ☐ No |
| Is the participant eligible for randomization? | ☐ Yes | ☐ No |
| Randomization assignment | ☐ Once Daily Treatment | ☐ Twice Daily Treatment |

| | |
|---|---|
| Signature: _____ | Date: ☐☐☐☐ ☐☐ ☐☐ (yyyy / mm / dd) |

CRU #044 TRIC VCI Plate #046 Phone Follow Up

**Subject ID:** Centre Subject ID **Date:** yyyy mm dd

# DAY 2 PHONE VISIT

| | | |
|---|---|---|
| 1. Subject contacted by phone on day 2 (if not reached, attempt to contact on each of days 3-6): | ☐ Yes | ☐ No |
| 2. Has the subject attempted to use the device: | ☐ Yes | ☐ No |
| 3. Does the subject report any problems with using the device: | ☐ Yes | ☐ No |
| 4. Is the subject willing to continue to participate in the study: | ☐ Yes | ☐ No |

| 5. Complete the visit checklist: | |
|---|---|
| Review device instructions | ☐ |
| Review diary instructions | ☐ |

**COMMENTS** (optional)

Signature: _____ Date: yyyy mm dd

CRU #044 TRIC VCI Plate #047 Phone Follow Up

**Subject ID:** ☐☐ ☐☐☐ (Centre / Subject ID) **Date:** ☐☐☐☐ ☐☐ ☐☐ (yyyy / mm / dd)

# DAY 15 PHONE VISIT

| | | |
|---|---|---|
| 1. Subject contacted by phone on day 15 (if not reached, attempt to contact on each of days 16-19): | ☐ Yes | ☐ No |
| 2. Has the subject attempted to use the device: | ☐ Yes | ☐ No |
| 3. Does the subject report any problems with using the device: | ☐ Yes | ☐ No |
| 4. Is the subject willing to continue to participate in the study: | ☐ Yes | ☐ No |

| 5. Complete the visit checklist: | |
|---|---|
| Review device instructions | ☐ |
| Review diary instructions | ☐ |

**COMMENTS** (optional)

Signature: _____ Date: ☐☐☐☐ ☐☐ ☐☐ (yyyy / mm / dd)

CRU #044 TRIC VCI Plate #048 Follow Up

**Subject ID:** Centre Subject ID **Date:** y y y y m m d d

# DAY 30 VISIT *(page 1 of 2)*

| MEDICAL HISTORY | | |
|---|---|---|
| 1. History of new prior transient ischemic attack since randomization? | ☐ Yes | ☐ No |
| If yes, then complete 1.a. and 1.b. | | |
| 1.a. Is there a history of more than one new ischemic attack? | ☐ Yes | ☐ No |
| 1.b. What was the date of the most recent prior transient attack? Date: y y y y m m d d | | |
| 2. History of new ischemic stroke since randomization: | ☐ Yes | ☐ No |
| If yes, then complete 2.a and 2.b. | | |
| 2.a. Is there a history of more than one new ischemic stroke? | ☐ Yes | ☐ No |
| 2.b. What was the date of the most recent ischemic stroke? Date: y y y y m m d d | | |
| 3. History of new intracerebral hemorrhage since randomization: | ☐ Yes | ☐ No |
| If yes, then complete 3.a and 3.b. | | |
| 3.a. Is there a history of more than one new intracerebral hemorrhages? | ☐ Yes | ☐ No |
| 3.b. What was the date of the most recent intracerebral hemorrhage? Date: y y y y m m d d | | |
| 4. History of new stroke of unknown type since randomization: | ☐ Yes | ☐ No |
| If yes, then complete 4.a and 4.b. | | |
| 4.a. Is there a history of more than one new stroke of unknown type? | ☐ Yes | ☐ No |
| 4.b. What was the date of the most recent stroke of unknown type? Date: y y y y m m d d | | |

CRU #044 TRIC VCI Plate #049 Follow Up

**Subject ID:** | | | | | | Centre | Subject ID |

**Date:** | | | | | | | | yyyy | mm | dd |

## DAY 30 VISIT *(page 2 of 2)*

| Day 30 visit checklist | |
|---|---|
| Retrieve device | ☐ |
| Retrieve patient diary | ☐ |

Signature: _____ Date: | | | | | | | | yyyy | mm | dd |

CRU #044 TRIC VCI Plate #050 End

**Subject ID:** | | | | | | Centre | Subject ID

**Date:** | | | | | | | | yyyy | mm | dd

# DAY 90 VISIT

| MEDICAL HISTORY | | |
|---|---|---|
| 1. History of new prior transient ischemic attack since randomization? | ☐ Yes | ☐ No |
| If yes, then complete 1.a. and 1.b. | | |
| 1.a. Is there a history of more than one new ischemic attack? | ☐ Yes | ☐ No |
| 1.b. What was the date of the most recent prior transient attack? Date: yyyy mm dd | | |
| 2. History of new ischemic stroke since randomization: | ☐ Yes | ☐ No |
| If yes, then complete 2.a and 2.b. | | |
| 2.a. Is there a history of more than one new ischemic stroke? | ☐ Yes | ☐ No |
| 2.b. What was the date of the most recent ischemic stroke? Date: yyyy mm dd | | |
| 3. History of new intracerebral hemorrhage since randomization: | ☐ Yes | ☐ No |
| If yes, then complete 3.a and 3.b. | | |
| 3.a. Is there a history of more than one new intracerebral hemorrhages? | ☐ Yes | ☐ No |
| 3.b. What was the date of the most recent intracerebral hemorrhage? Date: yyyy mm dd | | |
| 4. History of new stroke of unknown type since randomization: | ☐ Yes | ☐ No |
| If yes, then complete 4.a and 4.b. | | |
| 4.a. Is there a history of more than one new stroke of unknown type? | ☐ Yes | ☐ No |
| 4.b. What was the date of the most recent stroke of unknown type? Date: yyyy mm dd | | |

CRU #044 TRIC VCI Plate #051

☐ Randomization ☐ End
☐ Follow Up

**Subject ID:** ☐☐ ☐☐☐ *Centre* *Subject ID*

**Date:** ☐☐☐☐ ☐☐ ☐☐ *yyyy* *mm* *dd*

## COGNITIVE SCORES *(page 1 of 2)*

| | | | |
|---|---|---|---|
| Trail-making part A completed: | ☐ Yes | ☐ No | ☐ Other:_____ |
| Trail-making part A time to completion (seconds): | ☐☐☐ | | |
| Trail-making part B completed: | ☐ Yes | ☐ No | ☐ Other:_____ |
| Trail-making part B time to completion (seconds): | ☐☐☐ | | |
| 10-item word list learning completed: | ☐ Yes | ☐ No | ☐ Other:_____ |
| Trial 1 immediate recall: | ☐☐ | | |
| Trial 1 intrusions: | ☐☐ | | |
| Trial 2 immediate recall: | ☐☐ | | |
| Trial 2 intrusions: | ☐☐ | | |
| Trial 3 immediate recall: | ☐☐ | | |
| Trial 3 intrusions: | ☐☐ | | |
| Letter A fluency completed: | ☐ Yes | ☐ No | ☐ Other:_____ |
| Letter A fluency number of words: | ☐☐ | | |
| Letter S fluency completed: | ☐ Yes | ☐ No | ☐ Other:_____ |
| Letter S fluency number of words: | ☐☐ | | |
| Animal fluency completed: | ☐ Yes | ☐ No | ☐ Other:_____ |
| Animal fluency number of words: | ☐☐ | | |

CRU #044 TRIC VCI Plate #052

☐ Randomization ☐ End
☐ Follow Up

**Subject ID:** ☐☐ ☐☐☐ (Centre / Subject ID)

**Date:** ☐☐☐☐ ☐☐ ☐☐ (yyyy / mm / dd)

## COGNITIVE SCORES *(page 2 of 2)*

| | | | |
|---|---|---|---|
| Vegetable fluency completed: | ☐ Yes | ☐ No | ☐ Other:_____ |
| Vegetable fluency number of words: | ☐☐ | | |

| | | | |
|---|---|---|---|
| 10-item word list delayed recall completed: | ☐ Yes | ☐ No | ☐ Other:_____ |
| Delayed recall correct: | ☐☐ | | |
| Delayed recall intrusions: | ☐☐ | | |

Signature: _____ Date: ☐☐☐☐ ☐☐ ☐☐ (yyyy / mm / dd)

CRU #044 TRIC VCI Plate #053

☐ Randomization ☐ End
☐ Follow Up

**Subject ID:** ☐☐ ☐☐☐ (Centre / Subject ID)

**Date:** ☐☐☐☐ ☐☐ ☐☐ (yyyy / mm / dd)

# MRI TRANSMITTAL

| | |
|---|---|
| Date of MRI: | ☐☐☐☐ ☐☐ ☐☐ (yyyy / mm / dd) |
| MRI transmitted: | ☐ Yes ☐ No |

If no, give reason:

- ☐ No longer participating in the study (study termination CRF should also have been completed)
- ☐ Participant declined
- ☐ Not completed due to claustrophobia
- ☐ MRI contraindication
- ☐ MRI technical problem
- ☐ Other reason:_____

Signature:_____ Date: ☐☐☐☐ ☐☐ ☐☐ (yyyy / mm / dd)

CRU #044 TRIC VCI Plate #054 End

**Subject ID:** ☐☐ ☐☐☐ (Centre / Subject ID) **Date:** ☐☐☐☐ ☐☐ ☐☐ (yyyy / mm / dd)

# STUDY TERMINATION

| Subject has ceased to participate in TRIC VCI: | ☐ Yes |
|---|---|

**Please indicate reason:**

## Subject Adherence

- ☐ No device sessions for three or more consecutive days
- ☐ Declined to continue because of device-related discomfort
- ☐ Declined to continue for other reasons

Indicate reason: _____

## Contraindications to RIC

- ☐ Diagnosed with deep venous thrombosis of the upper or lower extremity, or other deep veins
- ☐ Upper arm skin breakdown or rash
- ☐ Arm surgery
- ☐ Initiated treatment with anticoagulant
- ☐ Poorly controlled blood pressure (mean values greater than 180 mmHg systolic)
- ☐ Other physician-determined contraindication to continuing treatment with RIC

Indicate the condition: _____

## Medical Comorbidities

- ☐ New medical condition that in the judgement of the site physician precludes continued participation in the trial

Indicate the new medical condition:_____

☐ Died ☐☐☐☐ ☐☐ ☐☐ (yyyy / mm / dd)

*Signature of investigator confrms the Study Termination :* _____

***e-signature***
***iDataFax use only***

☐☐ : ☐☐ ☐☐☐☐ ☐☐ ☐☐ (hh : mm yyyy mm dd)

PI's printed first and last name: _____

CRU #044 TRIC VCI Plate #055

Pg#:

**Subject ID:** Centre Subject ID

**Date:** yyyy mm dd

# ADVERSE EVENTS

| | | | |
|---|---|---|---|
| AE Event # | Adverse Event term _____ | | |
| AE Start Date: | yyyy mm dd | | |
| AE End Date (or Continuing): | yyyy mm dd<br>Continuing | | |
| Outcome: | Fatal | Not recovered/ not resolved | Recovered w/sequelae |
| | Recovered w/o sequelae | Recovering/ resolving | |
| Severity/Grade: | Mild | Moderate | Severe |
| Is the Event Serious? | Yes (Complete SAE) | No | |
| Is the Event Expected? | Yes | No | |
| AE Treatment: | None | Medication(s) | Non-medication TX |
| Action Taken with Study Intervention: | None | Interrupted | Discontinued |
| | Device sessions reduced | Device sessions increased | Not Applicable |
| Attribution/Relatedness: | Definite | Probable | Possible |
| | Unlikely | Unrelated | |

CRU #044 TRIC VCI Plate #056

Pg#:

**Subject ID:** Centre Subject ID

**Date:** yyyy mm dd

# MedDRA CODING FOR ADVERSE EVENT (AE)

***(to be completed by coordinating site)***

| AE Event # | Site Adverse Event term |
|---|---|
| | Common sense Adverse Event term |
| AE Category:<br><br>(Please look up corresponding AE Category at :https://safetyprofiler-ctep.nci.nih.gov/) | |

| | Term | Code |
|---|---|---|
| System Organ Classes (SOC) | | |
| High Level Group Term (HLGT) | | |
| High Level Term (HLT) | | |
| Preferred Term (PT) | | |
| Lowest Level Term (LLT) | | |

CRU #044 TRIC VCI Plate #057

Pg#: ☐

**Subject ID:** ☐☐ ☐☐☐ (Centre / Subject ID) **Date:** ☐☐☐☐ ☐☐ ☐☐ (yyyy / mm / dd)

## SERIOUS ADVERSE EVENTS (SAE) *(page 1 of 2)*

| | |
|---|---|
| SAE Event # ☐ | Serious Adverse Event term _____ |
| Report Type | ☐ Initial Report<br>☐ Follow-up Report F/U Report # ☐<br>☐ Final Report |
| SAE Classification: | ☐ Fatal (resulted in death) |
| | ☐ A life-threatening occurrence |
| | ☐ Requires inpatient hospitalization or prolongation of existing hospitalization |
| | ☐ Results in persistent or significant disability/incapacity |
| | ☐ Results in congenital anomaly/birth defect |
| | ☐ A significant medical incident that, based upon appropriate medical judgment, may jeopardize the subject and require medical or surgical intervention to prevent one of the outcomes listed above. |
| | ☐ Loss of confidentiality that results in criminal or civil liability for participation or damage to financial standing, employability, insurability or reputation of the participant |
| SAE Start Date: | ☐☐☐☐ ☐☐ ☐☐ (yyyy / mm / dd) |
| SAE End Date (or Continuing): | ☐☐☐☐ ☐☐ ☐☐ (yyyy / mm / dd)<br>☐ Continuing |
| Grade: | ☐ Mild ☐ Moderate ☐ Severe<br>☐ Life Threatening ☐ Death (Fatal) |
| Is the Event Expected? | ☐ Yes ☐ No |

CRU #044 TRIC VCI Plate #058

Pg#:

**Subject ID:** Centre Subject ID

**Date:** y y y y m m d d

# SERIOUS ADVERSE EVENTS (SAE) *(page 2 of 2)*

| | |
|---|---|
| Attribution/Relatedness: | ☐ Definite ☐ Probable ☐ Possible ☐ Unlikely ☐ Unrelated |
| Outcome: | ☐ Fatal ☐ Not recovered/ not resolved ☐ Recovered w/sequelae ☐ Recovered w/o sequelae ☐ Recovering/ resolving |
| Lead Site Notified Date: | y y y y m m d d |
| Local IRB/REB Notified Date: | y y y y m m d d |
| Narrative/Details: | _____ |

*Signature of investigator confrms the reported SAE :* _____

***e-signature***
***iDataFax use only***

h h : m m y y y y m m d d

PI's printed first and last name: _____

CRU #044 TRIC VCI Plate #059

Pg#:

**Subject ID:** Centre Subject ID

**Date:** yyyy mm dd

# SAFETY ADJUDICATION (SAE)

## REPORT INFORMATION

| | |
|---|---|
| Serious Adverse Event Name | _____ |
| SAE Start Date | yyyy mm dd |
| SAE End Date (or Continuing): | yyyy mm dd ☐ Continuing |
| Report Type | ☐ Initial Report ☐ Follow-up Report F/U Report # ☐ ☐ Final Report |
| Outcome | ☐ Fatal ☐ Not recovered/ not resolved ☐ Recovered w/sequelae ☐ Recovered w/o sequelae ☐ Recovering/ resolving |

## Is the Event

| | | |
|---|---|---|
| **Serious**? | ☐ Yes | ☐ No |
| Probably or definitely **Related** to the study device? | ☐ Yes | ☐ No |
| Is the event **expected**? | ☐ Yes | ☐ No |

## COMMENTS *(optional)*

Adjudication done by: _____
*(Print Name)*

CRU #044 TRIC VCI Plate #060

Pg#:

**Subject ID:** Centre Subject ID

**Date:** yyyy mm dd

# PROTOCOL DEVIATION

- ☐ Randomization Error
- ☐ Missed follow up visit:
- ☐ Follow up visit occurred outside of study window
- ☐ Incomplete follow up visit?
- ☐ Other: _____

Details:

_____

_____

_____

CRU #044 TRIC VCI Plate #061

Pg#:

**Subject ID:** Centre Subject ID

**Date:** yyyy mm dd

# PROTOCOL VIOLATION

- ☐ Enrolment does not comply with Inclusion Criteria
- ☐ Enrolment does not comply with Exclusion Criteria
- ☐ Failure to obtain Informed Consent
- ☐ Failure to report a Serious Adverse Event to the local IRB/REB and Sponsor
- ☐ Improper breaking of the blind
- ☐ Failure to report unanticipated problem involving the risks to participants or others to the IRB/REB and Sponsor
- ☐ Participant stopped treatment early
- ☐ Other: _____

CRU #044 TRIC VCI Plate #062

Pg#:

**Subject ID:** Centre Subject ID

**Date:** yyyy mm dd

# MEDICATIONS LIST

Medication list (list all, including any antiplatelet drugs with dose and frequency

| | |
|---|---|
| Medication Name: _____ | Dose: . |
| Indication: _____ | Units: ☐ mg ☐ mcg ☐ mL ☐ cc ☐ IU ☐ mEq ☐ oz ☐ tsp ☐ tbl ☐ gtt |
| Route: | ☐ po ☐ pr ☐ sub-q ☐ sub-lingual ☐ IM ☐ IV ☐ Patch ☐ Topical ☐ Nasal ☐ Other: _____ |
| Frequency: | ☐ OD ☐ BID ☐ TID ☐ QID ☐ PRN ☐ Other: _____ |
| Start Date: | yyyy mm dd |
| End Date: | yyyy mm dd ***OR*** ☐ Unable to determine |

| | |
|---|---|
| Medication Name: _____ | Dose: . |
| Indication: _____ | Units: ☐ mg ☐ mcg ☐ mL ☐ cc ☐ IU ☐ mEq ☐ oz ☐ tsp ☐ tbl ☐ gtt |
| Route: | ☐ po ☐ pr ☐ sub-q ☐ sub-lingual ☐ IM ☐ IV ☐ Patch ☐ Topical ☐ Nasal ☐ Other: _____ |
| Frequency: | ☐ OD ☐ BID ☐ TID ☐ QID ☐ PRN ☐ Other: _____ |
| Start Date: | yyyy mm dd |
| End Date: | yyyy mm dd ***OR*** ☐ Unable to determine |

Signature: _____ Date: yyyy mm dd

CRU #044 TRIC VCI Plate #063 Randomization

**Subject ID:** [ ][ ] [ ][ ][ ] *Centre* *Subject ID*

**Date:** [ ][ ][ ][ ] [ ][ ] [ ][ ] *yyyy* *mm* *dd*

# DEVICE PROVISION

| | | | |
|---|---|---|---|
| 1. Randomization and device provision checklist: | ☐ Subject randomized | | |
| | ☐ Device provided | | |
| | ☐ Device instructions provided | | |
| | ☐ Subject diary provided | | |
| | ☐ Device training provided | | |
| 2. First treatment cycle: | ☐ Completed | ☐ Not completed/not tolerated | |
| **If not completed, then subject will not continue in the study. Complete CRF Study Drop Out.** | | | |
| 3.Treatment-related discomfort: Show the Numeric Pain Rating Scale/Wong-Baker FACES Pain Rating Scale to the subject, instruct the subject on how to use it, and record: | | | |
| | 3.a. MAXIMUM pain during the treatment cycle: | [ ][ ] [range 0-10] | |
| | 3.b. Pain level during the last cuff inflation of the cycle: | [ ][ ] [range 0-10] | |
| 4. Symptoms reported during treatment (check all that apply): | | | |
| Was the treatment painful? | ☐ Yes | ☐ No | ☐ Not sure |
| Was there tingling (paresthesia)? | ☐ Yes | ☐ No | ☐ Not sure |
| 5. Other symptoms during treatment: | | | |
| _____ | | | |
| _____ | | | |
| 6. Is subject willing to continue in the study: | ☐ Yes | ☐ No | |
| **If "No", then subject will not continue in the study. Complete CRF Study Drop Out.** | | | |

Signature:_____ Date: [ ][ ][ ][ ] [ ][ ] [ ][ ] *yyyy* *mm* *dd*

## SUPPLEMENTARY FILE 3: TRIC-VCI TRIAL MANAGEMENT

### Study coordination

The trial will be organized by an executive committee principally centred in Calgary at the Calgary Stroke Program (Hotchkiss Brain Institute, University of Calgary and Department of Clinical Neurosciences). The overall PI for the trial will be Eric Smith. The Financial and Contracts Manager will be Anna Charlton. The Clinical Nursing Coordinator will be Karyn Fischer. The safety of the trial will be overseen by an independent Data Safety and Monitoring Board (DSMB). A Steering Committee will manage the day-to-day activities of the trial. Data will be managed by the University of Calgary Clinical Research Unit. Neuroimaging data will be managed by the Calgary Image Processing and Analysis Center (CIPAC) of Alberta Health Services.

### Trial Steering Committee

The Steering Committee will consist of the trial co-investigators and will be chaired by the trial principal investigator. Decisions will be made primarily by consensus, but in the absence of consensus they will be made by majority vote with the Chair serving as tie-breaker in case of tie votes. The Financial and Contracts Manager and Clinical Nursing Coordinator will attend Steering Committee meetings as non-voting members. Steering Committee teleconferences will be held no less frequently than once per quarter.

### Publications Committee

The Steering Committee will also act as the publications committee. Steering Committee members will be invited to contribute as coauthors on study papers. All authors must meet International Committee of Medical Journal Editor criteria for authorship. Proposals for ancillary papers will be reviewed and approved by the Steering Committee.

### Data processing

All imaging, evaluation forms, reports, and other records that leave the site are identified only by the site and subject number to maintain subject confidentiality. All records are kept in a locked file cabinet. Clinical information is not released without written permission of the subject, except as necessary for monitoring by IRB/REB, Health

All study investigators at the clinical sites must ensure that the confidentiality of personal identity and all personal medical information of study participants are maintained at all times. Federal legislation in Canada (Personal Information Protection and Electronic Documents Act PIPEDA), and provincial legislation (eg. Health Information Act HIA in Alberta) where applicable, must be followed. Additionally, any U.S. clinical sites must follow privacy obligations to study participants under the Health Insurance Portability and Accountability Act (HIPAA). European or Asian/Australasian sites must conform to local privacy and confidentiality law and custom. On the CRFs and other study documents or image materials submitted to the CRU, the subjects are identified only by study identification code.

Personal medical information may be reviewed for the purpose of verifying data recorded in the CRF by the site monitors. Other properly authorized persons, such as the regulatory authorities, may also have access to these records. Personal medical information is always treated as confidential.

**Audit and inspection**

The Sponsor-Investigator and any Participating Site Investigators should understand that source documents for this trial should be made available to appropriately qualified personnel from the Sponsor-Investigator or designee after appropriate notification. The verification of the CRF data must be by direct inspection of source documents.

Any Participating Site Investigators shall supply the Sponsor-Investigator on request with any required background data from the study documentation or clinic records. This is particularly important when CRFs are illegible or when errors in data transcription are suspected. In case of special problems and/or governmental queries or requests for audit inspections, it is also necessary to have access to the complete study records, provided that subject confidentiality is protected.

**Archiving**

The Sponsor-Investigator (and any Participating Site Investigators) must keep both (1) [illegible] clinical trial regulation. For example, at the University of Calgary, for non-Health Canada regulated studies, that period is 5 years from the time of official closure of the study. After that period of time the documents may be destroyed, subject to local regulations.

Data sharing policies will follow the spirit of the National Institute of Health (NIH) policy [http://grants2.nih.gov/grants/policy/data_sharing/data_sharing_guidance.htm]. A similar policy is in place at the Canadian Institutes of Health Research (CIHR). In addition, the Executive Committee will follow the CIHR guidelines on public access to trial results and make the results available as free-access using PubMed. Upon completion of the trial, a public use database will be prepared by stripping any and all personal identifiers. The public use database, consisting of several data files, should contain: (1) baseline and demographic characteristics; (2) outcomes assessments; (3) MRI data; (4) cognitive data; (5) concomitant medications; and (6) adverse events. Each data file is made available as a formatted text file or other electronic format. The data files are distributed along with the

[illegible] available to the public one year after completion of follow-up for the last subject.

SPIRIT

STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

| Section/item | Item No | Description | Addressed on page number |
|---|---|---|---|
| **Administrative information** | | | |
| Title | 1 | Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym | 1 |
| Trial registration | 2a | Trial identifier and registry name. If not yet registered, name of intended registry | 8 |
| | 2b | All items from the World Health Organization Trial Registration Data Set | N/A |
| Protocol version | 3 | Date and version identifier | 8 |
| Funding | 4 | Sources and types of financial, material, and other support | 27 |
| Roles and responsibilities | 5a | Names, affiliations, and roles of protocol contributors | 1, 27 |
| | 5b | Name and contact information for the trial sponsor | 1 |
| | 5c | Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities | 27 |
| | 5d | Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee) | _Supplement 5 |

| | | | |
|---|---|---|---|
| **Introduction** | | | |
| Background and rationale | 6a | Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention | 5-7 |
| | 6b | Explanation for choice of comparators | 7 |
| Objectives | 7 | Specific objectives or hypotheses | 7 |
| Trial design | 8 | Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory) | 8 |
| **Methods: Participants, interventions, and outcomes** | | | |
| Study setting | 9 | Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained | 13 |
| Eligibility criteria | 10 | Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists) | 10 |
| Interventions | 11a | Interventions for each group with sufficient detail to allow replication, including how and when they will be administered | 8-9 |
| | 11b | Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease) | 9 |
| | 11c | Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests) | 11 |
| | 11d | Relevant concomitant care and interventions that are permitted or prohibited during the trial | 10 |
| Outcomes | 12 | Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended | 12 |
| Participant timeline | 13 | Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure) | 12 |

| | | | |
|---|---|---|---|
| Sample size | 14 | Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations | 12 |
| Recruitment | 15 | Strategies for achieving adequate participant enrolment to reach target sample size | 12 |
| **Methods: Assignment of interventions (for controlled trials)** | | | |
| Allocation: | | | |
| Sequence generation | 16a | Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions | 9 |
| Allocation concealment mechanism | 16b | Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned | 9 |
| Implementation | 16c | Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions | 16 |
| Blinding (masking) | 17a | Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how | 9 |
| | 17b | If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial | 9 |
| **Methods: Data collection, management, and analysis** | | | |
| Data collection methods | 18a | Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol | 10-11, Supplement 2 |
| | 18b | Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols | 12 |

| | | | |
|---|---|---|---|
| Data management | 19 | Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol | 16, supplement 5 |
| Statistical methods | 20a | Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol | 14 |
| | 20b | Methods for any additional analyses (eg, subgroup and adjusted analyses) | 14 |
| | 20c | Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation) | 15 |
| **Methods: Monitoring** | | | |
| Data monitoring | 21a | Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed | 14, supplement 5 |
| | 21b | Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial | not applicable |
| Harms | 22 | Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct | 18 |
| Auditing | 23 | Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor | 17 |
| **Ethics and dissemination** | | | |
| Research ethics approval | 24 | Plans for seeking research ethics committee/institutional review board (REC/IRB) approval | 16 |
| Protocol amendments | 25 | Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators) | 16 |

| | | | |
|---|---|---|---|
| Consent or assent | 26a | Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32) | 16 |
| | 26b | Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable | 16 |
| Confidentiality | 27 | How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial | 16 |
| Declaration of interests | 28 | Financial and other competing interests for principal investigators for the overall trial and each study site | 16 |
| Access to data | 29 | Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators | 16 |
| Ancillary and post-trial care | 30 | Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation | not applicable |
| Dissemination policy | 31a | Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions | 18 |
| | 31b | Authorship eligibility guidelines and any intended use of professional writers | supplement 5 |
| | 31c | Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code | 18 |
| **Appendices** | | | |
| Informed consent materials | 32 | Model consent form and other related documentation given to participants and authorised surrogates | supplement 4 |
| Biological specimens | 33 | Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable | supplement 2 |

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.

BMJ Open

# Trial of Remote Ischaemic Pre-Conditioning in Vascular Cognitive Impairment (TRIC-VCI): Protocol for a randomised controlled trial



| | |
|---|---|
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# Trial of Remote Ischaemic Pre-Conditioning in Vascular Cognitive Impairment (TRIC-VCI): Protocol for a randomised controlled trial

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**Tables:** 3
**Figures:** 1
**Supplementary Files:** 5

**Key words**: clinical trial, vascular dementia, remote ischemic conditioning

## ABSTRACT

**Introduction:** Cerebral small vessel disease (cSVD) accounts for 20-25% of strokes and is the commonest cause of vascular cognitive impairment (VCI). In an animal VCI model, inducing brief periods of limb ischaemia-reperfusion reduces subsequent ischaemic brain injury with remote and local protective effects, with hindlimb remote ischaemic conditioning (RIC) improving cerebral blood flow, decreasing white-matter injury, and improving cognition. Small human trials suggest RIC is safe and may prevent recurrent strokes. It remains unclear what doses of chronic daily RIC are tolerable and safe, whether effects persist after treatment cessation, and what parameters are optimal for treatment response.

**Methods and Analysis:** This prospective, open-label, randomised controlled trial (RCT) with blinded endpoint assessment and run-in period, will recruit twenty-four participants, randomised to one of two RIC intensity groups: one arm treated once daily or one arm twice daily for 30 consecutive days. RIC will consistent of 4 cycles of blood-pressure (BP) cuff inflation to 200 mmHg for 5-minutes followed by 5-minutes deflation (total 35-minutes). Selection criteria include:age 60-85, evidence of cSVD on brain CT/MRI, Montreal Cognitive Assessment (MoCA) score 13-24, and preserved basic activities of living. Outcomes will be assessed at 30-days and 90-days (60-days after ceasing treatment). The primary outcome is adherence (completing ≥80% of sessions). Secondary safety/tolerability outcomes include the percent of sessions completed and pain/discomfort scores from patient diaries. Efficacy outcomes include changes in cerebral blood flow (per arterial spin-label MRI), white-matter hyperintensity volume, diffusion tensor imaging, MoCA and Trail-Making tests.

**Ethics and Dissemination:** Research Ethics Board approval has been obtained. The results will provide information on feasibility, dose, adherence, tolerability, and outcome measures that will help design a phase 2b RCT of RIC, with the potential to prevent VCI. Results will be disseminated through peer-reviewed publications, organisations and meetings.

**Registration Details:** NCT04109963; Pre-results

## ARTICLE SUMMARY

### Strengths and limitations of this study

- This trial will enrol patients using established neuroimaging criteria for the diagnosis of cerebral small vessel disease (cSVD), ensuring a valid sample of the target condition.
- Patients will be enrolled into two active comparator groups of remote ischemic pre-conditioning (RIC), with the primary goal of comparing the tolerability of different doses.
- The use of intent-to-treat analysis, pre-specified primary and secondary outcomes, and candidate biomarkers for monitoring treatment response will improve upon previous small studies of remote ischaemic pre-conditioning in cSVD; however, the lack of a non-treated or sham control group means that only within-patient changes can be analyzed.
- The use of a 60-day wash-out period after 30-days of treatment will help clarify the persistence of any RIC-related treatment effects.
- Participants and healthcare providers will not be blinded to the intervention, but endpoint assessment will be blinded to treatment allocation.

## INTRODUCTION

Cerebral small vessel disease (cSVD) is the commonest cause of vascular cognitive impairment (VCI), accounting for about 30% of all cases of dementia in community-based neuropathological studies.[1-3] cSVD can be identified on magnetic resonance imaging (MRI) using markers like small subcortical infarcts, lacunes, and white matter hyperintensities (WMHs).[2] cSVD patients have frequent, small brain infarcts, making this an ideal condition to study an intervention to condition the brain to resist ischaemia.[4 5] Although each new infarct is insidious and may not have an easily identified acute presentation, over time the cumulative burden leads to accelerated cognitive decline.[6 7] There are no proven therapies for preventing cSVD progression.[8] Strategies that can be safely applied early in the disease course would be particularly desirable.[9]

Experimentally inducing brief periods of ischaemia-reperfusion that do not result in tissue injury before an ischaemic event can reduce subsequent injury.[10] This process, known as ischaemic preconditioning, is thought to induce an endogenous protective environment, consisting of humoral and neuronal-mediated responses that promote cell survival/repair and dampen apoptotic/inflammatory pathways, mitigating ischaemic injury.[11] These protective mechanisms do not seem organ-specific, exerting systemic and remote protective effects; thus, remote ischaemic pre-conditioning (RIC) applied to a limb can promote tolerance to cerebral ischaemia.[10] The RIC stimulus appears to precipitate not only an early phase of short-term metabolic, energy utilization, and blood-flow changes lasting a few hours, but also a late phase of longer-lasting changes in gene expression, inflammatory, and oxidative pathways (16-96 hours post-RIC).[12] The exact mechanisms for signal transmission from the periphery to the brain to protect against ischaemia remain unclear, so there is uncertainty regarding the optimal

biomarkers of RIC. Candidate biomarkers include circulating nitrite, heat shock protein 27, microRNA-144, and interleukin-10.[13-16]

In a bilateral carotid occlusion model of VCI in mice, chronic daily RIC demonstrated increased angiogenesis (capillary density), cerebral flood flow, and preservation of white matter myelination at 1-month and 4-months.[17] In humans, RIC has been trialled for percutaneous coronary intervention (PCI) in the setting of acute myocardial infarction (MI),[18 19] elective PCI,[19] and cardiac surgery.[20] RIC has also been studied in the past few years in cerebrovascular disease, mostly applied to the upper-limb but some in the lower-limb,[21-26] and in several studies of peri-/post-conditioning (happening after ischaemic/haemorrhagic injury).[27-29] Bilateral upper-limb RIC protects against recurrent stroke in intracranial arterial stenosis.[22] A systematic review of RIC included three trials (371 participants) for ischaemic stroke prevention and four trials (364 participants) for ischaemic stroke treatment, and found low-quality evidence that RIC reduces recurrent stroke risk in patients with intracerebral artery stenosis and reduces stroke severity in patients undergoing carotid stenting.[30] There is also preliminary evidence of efficacy for this therapy in cSVD. A trial of 17 patients with cSVD randomised to RIC or sham-RIC reported improved mean flow velocity of the middle cerebral artery, lower dizziness handicap inventory score, and lower post-treatment WMH volume in the RIC group.[23] A trial in 36 patients with cSVD reported a significant reduction in WMH volume at 1-year compared to sham-RIC and a significant difference on visuospatial and executive function sections of the Montreal Cognitive Assessment (MoCA), though there was no significant change in the number of lacunes.[24]

Prior studies of RIC in cSVD have been small and essentially hypothesis-generating, and several uncertainties remain. First, the required “dose” of RIC sessions to observe a favourable effect is uncertain: a number of published studies have used bilateral upper-arm RIC twice daily,[22 24] but if similar results are obtained with once-daily and/or single upper-arm sessions,

this would be especially appealing for patients and facilitate treatment adoption. Importantly, human[31] and animal model[32 33] studies show that single-limb RIC with only 3-4 cycles can reduce end-organ ischaemic damage. As there are few human data to guide dose choices, the most comprehensive dose-finding data comes from an animal study[33] which found that more than one limb, more than four cycles, and more than 5-minutes of ischaemia conferred no additional reductions in infarct size in a mouse model of acute MI. Second, most published studies have reported exceptionally high patient compliance (>80%), even with bilateral upper-arm, twice-daily sessions – requiring at least 100-minutes daily, during which they can do little meaningful activity. It is uncertain whether similarly high compliance can be expected in the trial target population of persons with cognitive impairment. Third, the persistence of treatment effects beyond RIC cessation – as suggested by the "late phase" of RIC-related physiological changes per laboratory studies[17] – remains to be demonstrated. The aforementioned mouse model of bilateral carotid occlusion showed similar efficacy of RIC in mice receiving 1-month or 4-months of therapy,[17] but it is unclear if such persistence can be seen in humans. Fifth, prior cSVD trials (including of non-RIC treatments) have suffered from common methodological problems including lack of neuroimaging for diagnosis/classification, low-quality trial design (lack of intent-to-treat analysis or pre-specified primary outcomes, failure to account for multiple comparisons), and lack of biomarkers for monitoring and treatment response.[34]

Therefore, we propose an early phase trial to lay the foundation for a research program to further investigate the effect of RIC on prevention of cognitive decline caused by brain infarction from cSVD. We will examine whether different doses of daily RIC performed for 1-month are tolerable and safe, whether they result in improved cerebral blood flow (CBF), and whether the biomarker effects of 1-month of treatment are sustained at 3-months.

## METHODS AND ANALYSIS

### Study design

TRIC-VCI will be a prospective, open-label RCT with blinded endpoint assessment (PROBE)[35] and a run-in period, testing two regimens of RIC. The trial scheme is shown in **Figure 1**. The trial is registered at clinicaltrials.gov (NCT04109963). This manuscript described protocol version 2.0.

The trial will begin with a "run-in" period of 14-days in which all patients will be asked to perform once-daily single-arm RIC. Participants demonstrating >80% completion of treatment sessions (i.e. at least 12 of 14 sessions based on review of device records) will then be randomised to either: (1) RIC performed once-daily on one arm, or (2) RIC performed twice-daily on one arm.

### Intervention

Each RIC session will consist of 4 cycles of unilateral upper arm ischaemia for 5-minutes followed by reperfusion for another 5-minutes. The procedure will be performed by using an electric auto-control device (manufactured by Seagull Apps, Denmark) with cuffs that inflate to a pressure of 200 mmHg during the ischaemic period (**Figure 2**). This will first be demonstrated by a clinic-based nurse and will subsequently be performed by the patient at home, once- or twice-daily according to the randomised treatment assignment. The device records and documents each RIC cycle. The RIC process can be stopped at any time by the subject, if the subject experiences any major discomfort. Whereas the target inflation pressure of 200 mmHg is likely higher than what is needed to achieve occlusion in many patients, the same device with the same pressure settings was well tolerated by patients in a Danish study of acute stroke.[27]

The device will document each RIC cycle. Recordings will be obtained from the device at the in-person randomisation visit (to determine whether the participant is eligible to be randomised

based on adherence during the run-in period) and 30-day visits. The proportion that complete the run-in period will be a secondary endpoint.

**Discontinuation from study treatment**

If any of the following criteria are met at any time, treatment will be discontinued:

1. Patient declares unwillingness to proceed with the intervention.
2. Treatment is interrupted for >48-hours for any reason.
3. Diagnosis of deep venous thrombosis (DVT) or pulmonary embolism (PE).
4. Surgery on the upper extremity is performed or clinically indicated prior to cessation of the 30-day active treatment period.
5. Initiation of anticoagulation is clinically indicated.
6. Patient develops any other serious adverse event deemed by the attending physician to merit cessation of RIC.

The time-point of discontinuation will be recorded as accurately as possible (using device data) to determine the total number of actual treatment days for each patient. All patients will be followed to the end of the study period and analyzed in their assigned treatment arm.

**Randomisation scheme**

All subjects will be enrolled in this study consecutively and randomised into the two treatment groups in a 1:1 ratio. Randomisation will use a web-based algorithm with treatment assignment allocated by web-based real-time interaction with the site. Treatment assignments will be made using the Permuted Blocks method with randomly selected block sizes of 2, 4, or 6.

**Methods for protecting against bias (blinding)**

Participant assignments will not be concealed from treating physicians or subjects.

Investigators and assessors responsible for evaluating the results of cognitive testing, activities of daily living (ADLs), neuroimaging, and plasma testing will be blinded to treatment assignment. After enrolment of each subject, the site will designate a blinded evaluator (declared in the randomisation form) to perform 30-day and 90-day follow-up evaluations. This individual cannot be involved in the participant's care and must remain blinded to treatment assignment. Participants will be instructed not to disclose their treatment group to evaluators. Neuroimaging end-points will be determined by the core imaging laboratory blinded to treatment allocation.

**Inclusion and exclusion criteria**

Full details of the inclusion and exclusion criteria are listed in **Table 1**. Briefly, we will enrol patients with mild vascular neurocognitive disorder, or the earlier stages of major vascular neurocognitive disorder. This will include patients with neuroimaging evidence of significant cSVD burden (as defined in **Table 1**), objective evidence of cognitive impairment (MoCA≤24) but independent in basic ADLs, and for whom concerns regarding cognition are expressed by the patient, caregiver, or referring clinician. To target patients in the milder range of cognitive impairment, we will exclude patients with MoCA<13.

Participants with small cortical infarcts will be allowed but patients with larger (>10mm axial diameter) cortical infarcts will be excluded. This is because large destructive lesions may confound study assessments of the impact of progressive cSVD by independently causing clinical disabilities (aphasia, anosognosia, etc) or by confounding neuroimaging processing pipelines. For similar reasons, we exclude patients with a prior history of stroke-related disability, who by definition will not meet our inclusion criterion of being independent for basic ADLs. Whereas all patients will meet inclusion criteria for demonstrating evidence of cSVD on CT/MRI, we will not require testing for biomarkers of Alzheimer's Disease in our study, with the understanding that some patients will have mixed dementia.

**Frequency and duration of follow-up**

After their initial recruitment into the study (screening visit), all patients will receive instruction on how to use the RIC device. They will be asked to perform RIC therapy once daily, in one arm, for a total of ≥14 days ("run-in" period). This will be followed by a telephone follow-up visit intended to assess and address tolerability and compliance issues at 1- to 3-days after beginning the run-in period, and to provide further education on how to use the device. Another in-person clinic visit may be scheduled, at the discretion of the site investigator, if further training and education are needed.

Patients demonstrating the required >80% completion of run-in period treatment sessions will proceed to randomisation. At the randomisation visit (occurring as soon as possible, but not sooner, than 14-days into the run-in period), patients who meet adherence targets will be randomly allocated to one of the 2 treatment groups. A telephone follow-up visit will be done 1-3 days after randomisation, to assess and address tolerability and compliance issues. A similar telephone visit will be performed at 15±3-days to further encourage compliance.

Patients will stop their assigned treatments on day 30±3 days post-randomisation, at which point they have an in-person follow-up visit. A final follow-up in-person visit will occur at 90±3 days post-randomisation (approximately 2-months free of RIC).

Near study close-out, participants and their care partners at the Calgary study site will be invited to participate in an exit interview in a group setting regarding their experiences in the trial. We will aim to include 4-6 participants with their care partners.

**Primary and secondary outcome measures**

The primary feasibility/compliance outcomes will be adherence rate at 30 days, defined as the percentage of sessions completed. Secondary safety/tolerability and efficacy endpoints are specified in **Table 2.** The main efficacy endpoints include change in cognitive test scores on the MoCA,[36] Trail-Making A and B,[37] Controlled Oral Word Association Test (COWAT),[38 39] and CERAD 10-item word list learning[40] at 30-days and 90-days, change in MRI peak skeletonized mean diffusivity of the white matter,[41] and change in WMH volume.

The specifications of how these outcome measures will be measured are presented in **Supplementary File 1.**

**Procedures and variables**

The schedule of procedures and variable collection for the trial is presented in **Table 3**. Details of study assessments at each visit are presented in **Supplementary File 2**. Cognitive testing and MRI will be done at randomization, 30-days, and 90-days. Each study participant will also have an informant, ideally one who lives with them or is a caregiver, who will provide important collateral data about their cognitive and behavioural status (via the AD8 informant questionnaire, IQCODE, and the MBI checklist) and daily activities (via the Bristol ADL Scale [BADLS] longitudinally).

**Sample size justification**

The selected sample size is based on the precision for measurement of the primary outcome (adherence rate), feasibility based on recruitment rate and funding, and the desire to avoid exposing an unnecessarily large number of trial participants to an intolerable treatment arm. With 12 subjects per study arm, if 83% adhere to the treatment arm (meeting our pre-specified outcome of ≥80% adherence) then we can predict with 95% confidence that the true adherence rate is 52-98%. This would provide enough confidence to proceed to a subsequent phase 2 study with a randomised sham control.

Sample size calculations for biomarker efficacy are based on the ability to restore more normal gray matter CBF in patients with VCI due to cSVD. Prior literature on CBF measurements in cSVD has recently been systematically reviewed[42]. Based on a prior study of cSVD VCI patients,[43] we estimate gray matter CBF will be 37.8±12.4mL/100g brain tissue/minute in cSVD and 55.8±12.4mL/100g/minute in age matched healthy controls. We estimate that RIC will restore 52% of normal CBF (i.e. an increase to 46.8mL/100g/minute), as seen in an animal model of VCI[17]. CBF can be measured with good precision using MRI PCASL (estimated within-subject coefficient of variation 4.1% based on two studies[44 45]). Based on these assumptions and two-tailed alpha=0.05, the current trial will provide >99% power to detect a mean increase of 9mL/100g/min CBF from baseline within each arm. For a future phase 2b study, a sample size of 32 in each arm would provide 80% power and a sample size of 42 in each arm would provide 90% power to determine whether RIC increases CBF by 9mL/100g/minute compared to a sham control. Since this is a relatively novel use of ASL, and our estimate for CBF increase are based on a small study sample with mild dementia,[43] our sample size estimation for the biomarker component must be interpreted with caution, and the CBF measure is best interpreted as an exploratory outcome.

**Recruitment strategy and projected recruitment rate**

Patients will be screened at specialty Stroke/TIA clinics and Cognitive clinics (generally staffed by neurologists, geriatricians, or psychiatrists) at each of the study sites. The initial screening can be done by clinicians as part of usual care, since a number of the evaluations needed to determine study eligibility (clinical history of cognitive symptoms, MoCA, and neuroimaging) are commonly used clinical tests recommended by Canadian clinical guidelines. We aim for a recruitment rate of 1 patient per month per site (5/month across all sites), aiming to achieve our target sample size of 24 in 7-8 months.

**Number of centers**

There are five participating sites across Canada: University of Calgary (lead site), University of British Columbia, McMaster University, University of Toronto, Western University.

**Proposed Analysis**

Primary and secondary outcomes will be compared between the two study groups (or in all subjects at the end of the run-in phase, as specified), with intent-to-treat analysis. To investigate the sustainability of changes at 90-days (60-days after ceasing RIC) and 30-days for relevant secondary outcomes, tests will compare the two treatment groups at 30-days and then the two treatment groups at 90-days. Given the relatively small sample size, normality assumptions will be based on prior literature and not testing within the trial data set.

The primary outcome, adherence rate at 30-days, will be calculated as: number of sessions completed / [number of sessions per day x number of scheduled days of therapy]). Subjects are expected to complete 27-33 days of therapy, per protocol. Fisher's exact test will be used to compare proportions completing ≥80% of assigned sessions. The mean number of sessions completed will be compared by analysis of variance (ANOVA).

The statistical test for each secondary outcome is specified in **Table 2**. If the linear mixed models planned for some of the variables do not converge, we will compare the difference from baseline to 30-/90-days in the two arms using the t-test or Wilcoxon rank-sum. Since our main motivation for implementing ASL in this study is to determine its suitability as an outcome measure for a larger subsequent trial, we will also examine the variation in ASL measurements across sites and within-person variation at each site.

For the qualitative exit interview with participants, an audio recording of the group session will be transcribed and analyzed for emerging themes regarding the ease of use of the RIC device, the quality of the user manual and other patient instructions, the tolerability of the treatment, and advice for conduct of future trials.

**Handling of missing data**

Baseline characteristics and treatment assignments of patients with and without missing data will be compared to identify significant differences that might affect the interpretation of results. Given the relatively small sample size, we will not perform multiple imputation on missing data.

**Subgroup analyses**

A priori subgroup analyses will include assessing tolerability and treatment effects by age, sex, self-reported physical activity level, and baseline burden of SVD. For secondary clinical outcomes of interest – MoCA, Trail-Making, COWAT, CERAD 10-item word list learning score, MBI checklist, and BADLS scores – analyses will be adjusted for the participants' respective baseline score on that measure, since these outcomes may be especially influenced by the baseline level of cognitive impairment.

**Patient and public involvement**

Patients and the public were not directly involved in the study design. However, the primary and secondary outcomes are focused on assessing the burden and tolerability of the intervention for patients, in preparation for larger-scale trials. As noted above, we will also conduct a qualitative interview near study close-out to obtain feedback from patients based on their experience, thereby giving them a voice in subsequent trial designs. Results will be disseminated through patients and study participants through our institution's social media platform and the website of the Canadian Consortium on Neurodegeneration (www.ccna-ccnv.ca).

## ETHICS AND DISSEMINATION

### Ethical Considerations

This protocol and the informed consent form (ICF) have been reviewed and approved by the Conjoint Health Research Ethics Board at the University of Calgary. A signed ICF must be obtained from the subject at the screening visit prior to the "run-in" period or any other study procedures (**Supplementary File 3**). The ICF describes the purpose of the study, the procedures to be followed, and the risks and benefits of participation. Consent will be obtained by a physician investigator or coinvestigator. Ethics approval, including for protocol and consent changes, is required by separate review boards at each study site. Declarations of competing interests are provided to the ethics boards and will be included with manuscript submissions.

### Data management

De-identified data will be housed and managed in a password-protected custom database at the University of Calgary Clinical Research Unit. The data will be supported by an FDA-compliant commercial database (iDATAFAX) which will allow electronic data capture (EDC) or fax-back data capture on a site-by-site basis. Sites will maintain patient identifiable source data in a secure location. The principal investigator (PI) and co-investigators will have access to the data.

### Data recording

The Sponsor-Investigator (and any Participating Site Investigators) will maintain adequate and accurate records to enable the conduct of the study to be fully documented and the study data to be subsequently verified. These documents are classified into two different separate categories: Investigator's Study File and Subject clinical source documents.

The Investigator's Study File will contain the protocol/amendments, Case Report Forms (CRFs) and Query Forms, institutional review board and governmental approval with correspondence,

all versions of ethics-approved ICFs, staff curriculum vitae and authorization forms and other appropriate documents/correspondence.

Subject clinical source documents would include subject hospital/clinic records, physician's and nurse's notes, appointment book, original laboratory reports, imaging reports, completed CRFs (**Supplementary File 4**), any relevant pathology and special assessment reports, signed ICFs, consultant letters, and subject screening and enrolment logs.

For each subject enrolled, a CRF will be completed and signed by the Sponsor-Investigator (and any Participating Site Investigator) or authorized delegate from the study staff. This also applies to records for those patients who fail to complete the study (even during a pre--randomisation screening period if a CRF was initiated). If a subject withdraws from the study, the reason must be noted on a CRF. If a subject is withdrawn from the study because of a treatment-limiting AE, thorough efforts will be made to clearly document the outcome.

**Monitoring**

All data will be monitored centrally by the coordinating center at the University of Calgary for accuracy and completeness. The initial performance-monitoring assessment will take place after the initial subject is enrolled, and the next assessment will take place at close-out. The close-out monitoring assessment will take place at completion of subject enrolment and protocol required follow-up visits at the performance site. Monitoring visits will be done remotely by teleconference, but the coordinating center reserves the right to conduct on-site monitoring at its discretion. The monitor will verify the adequacy of site facilities and staff, site recruitment, subject randomisation, ICFs, and the presence of regulatory documents. During the visit, any omissions/corrections to data submitted to the database are noted and queries are generated

by the monitor. At close-out, sites are instructed in the record retention of all trial documents. PIs will issue a final report to the ethics board.

Details on study coordination, the steering committee, data processing, audit and inspection, and archiving protocols are presented in **Supplementary File 5.**

**Safety and Adverse Events**

Adverse events should be reported as they occur on the CRF. Documentation must be supported by an entry in the subject's file. Each event should be described in detail along with start and stop dates, severity, relationship to the therapy as judged by the Investigator, action taken and outcome. Serious adverse events (SAEs) must be reported within 1 business day of the local investigator or outcome assessor's first awareness of its occurrence. SAEs will be reviewed by the trial medical monitor. Because this is not a regulatory trial, SAEs do not require reporting to Health Canada or other regulatory authorities. Because the adverse event profile of RIC has been quite benign in previous trials, we do not predict that there will be unexpected SAEs.

Safety outcomes of DVT/PE, arm neurovascular injury, and serious adverse events will be adjudicated by a medical monitor, an independent neurologist with experience in clinical trials, who will report these events to the Steering Committee.

**Data dissemination**

Results will be disseminated through peer-reviewed publications, professional organisations, and conferences. The de-identified study dataset and analysis code will be posted to the University of Calgary section of the PRISM dataverse at the time of publication of the main study results. The data will complement work by our basic/translational science collaborators

who will be conducting parallel animal studies to explore dose response relationships with various additional RIC regimens in greater granularity – which we are unable to do in our trial for practical reasons of cost and the available patient population.

The data from this trial will be used to inform decisions on study design for a subsequent phase 2b trial including: 1) the frequency (once or twice daily) of RIC, based on adherence and safety data, 2) the choice of clinical cognitive and functional tests and assessment scales, based on feasibility and reliability, and 3) the choice of biomarkers, based on feasibility, reliability, and sensitivity to change over time.

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## AUTHOR STATEMENT

AG assisted with the design of the study protocol, drafted the first version of the manuscript, and prepared subsequent revisions. PAB, DC, SEB, TSF, RF, VCH, ZI, LMM, CRM, DJS, MS, and RHS participated in the revisions of the study protocol, read and reviewed the manuscript, and approved the final version of the manuscript. EES conceived, designed, and supervised the study protocol, read and reviewed the manuscript, and approved the final version of the manuscript.

## DATA AVAILABILITY

The de-identified study dataset and analysis code will be posted to the University of Calgary section of the PRISM dataverse at the time of publication of the main study results.

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## CONFLICTS OF INTEREST

Dr. Ganesh has a patent pending for a system to deliver remote ischemic conditioning, not related to the device (or manufacturer) being used in this trial. Dr. Smith reports consulting fees from Alnylam Pharmaceuticals and Biogen; and royalties from UpToDate.

## TABLES

**Table 1. Inclusion and Exclusion Criteria for the TRIC-VCI study**

| Inclusion Criteria | Operationalized as: |
|---|---|
| 1. Evidence of cerebral small vessel disease on CT or MRI | Evidence of either:<br>1. Beginning confluent WMH (ARWMC[46] grade 2) on any slice on CT or MRI<br>OR<br>2. Two or more supratentorial subcortical infarcts |
| 2. Objective evidence of cognitive impairment | MoCA[36] score ≤24 |
| 3. Concern on the part of the patient, caregiver, or clinician that there has been a decline from previous level of cognitive functioning | AD8 questionnaire[47] (administered to informant) with 2 or more positive responses, or clinical judgement based on self report of participant or observations by examiner |
| 4. Independent with basic daily activities of living | BADLS[48] response (a) for questions 2, 4, 5, 6, 7, 8, 9, and 14. |
| 5. Age 60-85 | |
| **Exclusion Criteria** | |
| 1. Cortical infarcts larger than 10 mm axial diameter. | Based on site review of clinical CT or MRI |
| 2. Symptomatic ischemic or hemorrhagic stroke occurring within the last 90 days | |
| 3. Neuroimaging evidence of mass lesion, intracerebral haemorrhage, vascular malformation, or evidence of non-vascular disease such as hydrocephalus. | Based on site review of clinical CT or MRI. Microbleeds are allowed. |
| 4. Residence in long-term care facility. | |
| 5. Other significant neurological or psychiatric disease (e.g. multiple sclerosis). | |
| 6. Subject does not have a study partner who can provide corroborative information. | Partner is required to complete the BADLS and MBI-Checklist.[49] |
| 7. English or French is not sufficiently proficient for clinical assessment and neuropsychological testing. | |
| 8. Total score on the MoCA <13 | |
| 9. Unable to undergo MRI due to medical contraindications or inability to tolerate the procedure. | |
| 10. Co-morbid medical illness that in the judgment of the study investigator makes it unlikely that the participant will be able to complete three months of study follow-up. | |

| | |
|---|---|
| 11. On therapeutic anticoagulation with doses used for treatment of deep venous thrombosis, pulmonary embolism, or for stroke prevention in atrial fibrillation. | Lower dose anticoagulation for prevention of coronary artery disease, e.g. rivaroxaban 2.5 mg po bid, will be allowed. |
| 12. Significant bleeding diathesis. | Including but not limited to hemostatic disorder, platelet count <100 x $10^9$/L, INR >1.7, history of liver cirrhosis. |
| 13. Any symptomatic or previously known arm soft-tissue disease, vascular injury, or peripheral vascular disease. | Defined as patients with symptoms of vascular claudication or prior arterial thromboembolism in limbs. |
| 14. Hypertension with systolic blood pressure ≥180 mmHg despite medical treatment at the time of enrolment. | |
| 15. Planned revascularization (any angioplasty or vascular surgery) within the next three months. | |
| 16. Planned surgical procedure within the next three months. | |
| 17. Currently receiving an investigational drug or device by other studies | |

**Table 1 Legend:** ARWMC, Age-related White Matter Changes; BADLS, Bristol Activities of Daily Living Scale; CT, computed tomography; MBI checklist, mild behavioural impairment checklist; MoCA, Montreal Cognitive Assessment; MRI, magnetic resonance imaging.

**Table 2. Secondary endpoints for the trial and the statistical test to be used for each**

| Secondary safety/tolerability endpoints | Statistical test of choice |
|---|---|
| 1. Discontinuation prior to 30-days | Fisher's exact test |
| 2. Proportion completing the run-in period and entering the randomisation phase | Fisher's exact test |
| 3. Physical examination signs of tissue or neurovascular injury resulting from RIC treatment at 30-days | Fisher's exact test |
| 4. Development of symptomatic upper extremity deep vein thrombosis at 30-days and 90-days | Fisher's exact test |
| 5. Peak and end-cycle pain levels reported by the participant using the Visual Analog Scale during the 30-day treatment period | Repeated measures analysis with linear mixed models will be used to estimate the mean VAS per session, using all VAS data and including the subject as a random effects term to account for within-subject correlation. Peak and end VAS will be analyzed in separate models. The proportion with intolerable pain, defined as estimated mean VAS >8, will be compared by Fisher's exact test. Subjects with insufficient VAS data, defined as <3 recorded VAS peak or <3 recorded VAS end levels, will be excluded from these analyses |
| Secondary efficacy endpoints | |
| 1. Change in MRI WMH volume at 30-days and 90-days | Volumes at baseline and follow up will be logarithmically transformed (natural log) to give a more normal distribution. Then differences between each group will be compared using a linear mixed model |
| 2. Change in MRI diffusion tensor imaging (DTI) peak skeletonized mean diffusivity[41] (PSMD) at 30-days and 90-days | Linear mixed model, testing difference at 30-days and 90-days. |
| 3. Number of new MRI infarcts at 30-days and 90-days | Fisher's exact test |
| 4. Number of new MRI DWI-positive lesions at 30-days and 90-days | Fisher's exact test |
| 5. Change in MRI ASL gray matter cerebral blood flow at 30-days and 90-days | Linear mixed model, testing difference at 30-days and 90-days. |
| 6. Change in MoCA[36] score at 30-days and 90-days | Linear mixed model, testing difference at 30-days and 90-days |
| 7. Change in Trail-Making A and B[37] at 30-days and 90-days | Volumes at baseline and follow up will be logarithmically transformed (natural log) to give a more normal distribution. Linear mixed model, testing difference at 30-days and 90-days |

| | |
|---|---|
| 8. Change in Controlled Oral Word Association[38 39] score at 30-days and 90-days | Linear mixed model, testing difference at 30-days and 90-days. |
| 9. Change in CERAD 10-item word list learning[40] score at 30-days and 90-days | Linear mixed model, testing difference at 30-days and 90-days |
| 10. Change in total score on MBI Tracking Tool, adapted from the MBI Checklist[50], at 30-days and 90-days | Linear mixed model, testing difference at 30-days and 90-days |
| 11. Change in BADLS[48] at 30--days and 90-days | Linear mixed model, testing difference at 30-days and 90-days |
| 12. Difference in candidate blood biomarkers at 30-days and 90-days | Linear mixed model, testing difference at 30-days and 90-days |

**Table 3. Overview of the schedule of procedures and variable collection**

| | Visit | | | | | |
|---|---|---|---|---|---|---|
| | **Screening** | **Random-ization** | **Phone Fu** | **Phone Fu** | **F/u** | **End** |
| **Activity** | 0 | Within 30 d | 1-3 d | 15±3 | 30±3 | 90±3 |
| Written consent | ✓ | | | | | |
| Demographics | ✓ | | | | | |
| Medical history | ✓ | ✓ | | | ✓ | ✓ |
| Medications | ✓ | ✓ | | | ✓ | ✓ |
| Physical exam | ✓ | ✓ | | | ✓ | |
| NIH Stroke Scale | ✓ | ✓ | | | ✓ | ✓ |
| Hachinski ischaemic score | ✓ | | | | | |
| MoCA | ✓ | ✓ | | | ✓ | ✓ |
| Bristol Activities of Daily Living Scale | ✓ | ✓ | | | ✓ | ✓ |
| AD8 Informant Questionnaire | ✓ | | | | | |
| IQCODE | ✓ | | | | | |
| Inclusion/exclusion criteria | ✓ | | | | | |
| RIC device provision | ✓ | | | | | |
| RIC device training | ✓ | ✓ | ✓ | ✓ | | |
| Subject diary provision | ✓ | | | | | |
| Subject diary review | | ✓ | | | ✓ | |
| Adherence (device print out) | | ✓ | | | ✓ | |
| Randomisation | | ✓ | | | | |
| Cognitive tests | | ✓ | | | ✓ | ✓ |
| MBI Checklist | | ✓ | | | ✓ | ✓ |
| Blood draw | ✓ | ✓ | | | ✓ | ✓ |
| MRI | | ✓ | | | ✓ | ✓ |

## FIGURE LEGENDS

**Figure 1.** Trial design for the TRIC-VCI study

**Figure 2.** Device for applying remote ischemic conditioning (Seagull Aps, Denmark). The device applies four cycles of remote ischemic conditioning upon pressing the button. Device activations are recording, including the number of cycles. Systolic blood pressure, diastolic blood pressure, and pulse are displayed.

| Visit | Screening | Randomisation | Phone | Phone | End Treatment | End |
|---|---|---|---|---|---|---|
| **Time** | ≤-14 | 0 | 2±1 | 15±3 | 30±3 | 90±3 |
| **Measure-ments** | Eligibility | Feasibility<br>Safety/tolerability<br>Efficacy | | | Feasibility<br>Safety/tolerability<br>Efficacy | Efficacy |

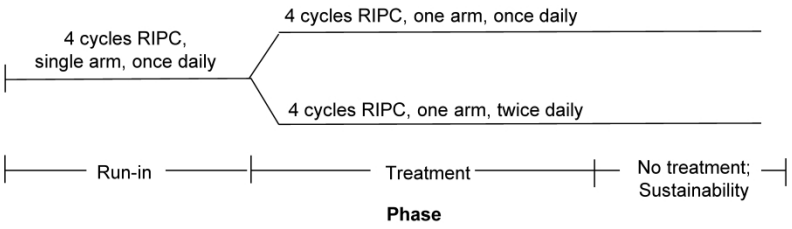


Figure 1. Trial design for the TRIC-VCI study.

159x76mm (1200 x 1200 DPI)


Figure 2. Device for applying remote ischemic conditioning (Seagull Aps, Denmark). The device applies four cycles of remote ischemic conditioning upon pressing the button. Device activations are recording, including the number of cycles. Systolic blood pressure, diastolic blood pressure, and pulse are displayed.

101x64mm (600 x 600 DPI)

**SUPPLEMENTARY FILE 1: HOW OUTCOME MEASURES WILL BE MEASURED**

| **Outcome Measure** | **Measurement or operationalized definition** |
|---|---|
| **Feasibility Outcomes** | **All measured at the point of randomization as well as at 1-month (including only randomized patients)** |
| Adherence – the number of sessions completed (maximum 30±2); good adherence defined as ≥80% completion | Determined by automated real-time recording of the RIC device. Study staff will print out the recording from the device at the time of follow-up. defined as the percentage of sessions completed (number of sessions completed / [number of sessions per day x number of scheduled days of therapy]. If the patient discontinues therapy prior to the 30 days, the denominator scheduled days of therapy will be defined as 30. |
| Discontinuation rate | Defined as:<br>1. Patient declares unwillingness to proceed with the intervention, OR<br>2. Patient develops serious adverse event deemed by attending physician to merit cessation of RIC. |
| **Safety and Tolerability Outcomes** | **All measured at the point of randomization as well as at 1-month (including only randomized patients)** |
| Any serious adverse event deemed by attending physician to merit cessation of RIC. | Will include arm tissue or neurovascular injury or upper extremity deep venous thrombosis. |
| Objective signs of tissue or neurovascular injury resulting from RIC treatment | Inspection by observers blinded to the study protocol which will include palpation of distal radial pulses, visual inspection for local edema, erythema, skin breakdown and/or other skin lesions, and palpation for tenderness. |
| Development of symptomatic upper extremity deep vein thrombosis | As demonstrated on extremity ultrasound, to be obtained only if clinically indicated by the attending physician based on follow-up examination of the upper limb. |
| Pain or discomfort | Rated on follow-up assessments using the Numeric Rating System NRS which requires participants to self-report an |

| | |
|---|---|
| | integer ranging from 0 (no pain) to 10 (worst imaginable pain).[45] To help participants choose the appropriate pain level, the Wong Baker FACES Pain scale[46] will be displayed along with the NRS. The Wong Baker scale has been validated in persons with cognitive impairment[47]. "Intolerable pain" will be defined as intra-subject mean NRS>8, corresponding with "hurts a whole lot" on the Wong Baker FACES Pain scale. |
| **Efficacy Outcomes** | **All measured at 1-month and 3-months** |
| Change in cerebral blood flow | Change in cerebral gray matter blood flow on arterial spin-label (ASL) MRI. |
| Change in MRI WMH volume | MRI FLAIR images will be processed for WMH volume using semi-automated Quantomo software (Cybertrials, Inc) at the University of Calgary Stroke Core Imaging Lab. A single blinded rater qualified by the Stroke Core Imaging Lab will measured WMH volume on the three scans from each trial subject, blinded to scan order. |
| Change in MRI DTI PSMD | A single assessor from the Stroke Core Imaging Lab will determine PSMD[42] on each scan, using the processing pipeline described at http://www.psmd-marker.com/, blinded to treatment status. |
| New brain infarct | A single neurologist or neuroradiologist qualified by the Stroke Core Imaging Lab will review each scan for chronic infarcts and new infarcts. Recent small subcortical infarcts and lacunar infarcts will be defined according to Standards for Reporting Vascular Changes on Neuroimaging (STRIVE)[2]. Cortical infarcts will be defined as areas of focal enchephalomalacia with T1 hypointensity and T2 hyperintensity in the distribution of a vascular territory. Small (<5 mm) cortical infarcts will be defined according to recent consensus criteria for "microinfarcts"[48]. |
| New DWI positive lesion | A single neurologist or neuroradiologist qualified by the Stroke Core Imaging Lab will review each scan for DWI |

| | |
|---|---|
| | positive lesions. Apparent Diffusion Coefficient (ADC) maps will be reviewed to exclude confounding T2 shine through from chronic lesions, but ADC hypointensity is not required to be present. Small DWI positive lesions (< 5 mm) will be defined according to recent consensus criteria for acute "microinfarcts"[48]. |
| Cognitive decline | Change in scores from pre- to post-treatment:<br>1. Mean change in total MoCA scores.<br>2. Proportion with decline in total MoCA ≥2 points.<br>3. Mean change in MoCA visuospatial/executive subscore.<br>4. Mean change in Trail-Making Test A and B scores. |
| Functional decline | Change in BADLS total score[41]. |
| Change in neuropsychiatric symptoms | Change in total score on the MBI Tracking Tool, adapted from the MBI Checklist[44]. |
| Candidate Biomarkers | All measured in venous blood:<br>1. Homocysteine<br>2. Circulating nitrite<br>3. Interleukin-10<br>4. Matrix metalloproteinase 2 and 9<br>5. TNF-alpha<br>6. Interferon gamma<br>7. MicroRNA-144<br>8. SDF-1-alpha<br>9. Heat shock protein 27 |

## SUPPLEMENTARY FILE 2: DETAILS OF STUDY ASSESSMENTS AT EACH VISIT

### Screening visit

At the first screening visit, patients who are deemed by the attending physician to potentially be eligible for the study will sign consent and then undergo a detailed clinical assessment to ensure that they meet inclusion criteria and do not meet any exclusion criteria. Participants who do not meet study selection criteria at the end of the visit will be deemed screen failures, will cease participation in the study, and will not be counted toward the target study sample size.

The screening visit assessment are:

- Demographic characteristics
- Medical histories, including vascular risk factors, previous history, concomitant medication, and family history
- Information about the participants' general levels of physical activity
- Physical examination including blood pressure assessment, NIH Stroke Scale (NIHSS)[49], examination of the arms for any severe soft tissue injury or evidence of ischemia that would be deemed a RIC contraindication.
- Hachinski Ischemic Score[50].
- Cognitive performance, using the MoCA.
- Informant reports of cognitive decline and functional status using BADLS, AD8, and IQCODE short form[51] questionnaires *(if patient does not attend with an informant, then the informant may be contacted by telephone or post to complete these assessments).* If there is a history of past symptomatic stroke, then the Rankin Focused Assessment will also be administered and used to determine the modified Rankin Scale score.
- Review of neuroimaging (CT or MRI) obtained clinically within the last year, to document neuroimaging eligibility criteria. CT or MRI are recommended by clinical consensus criteria and medical guidelines for diagnosis of stroke, cSVD, or neurocognitive disorders[52,53].

All patients meeting inclusion criteria will be invited to participate in the 14-day minimum run-in period. They will be taught how to use the RIC and will be observed performing a full session (4 cycles of ischemia and reperfusion) to ensure that they are using the device correctly, before being sent home with the device.

**Randomization visit**

After the 14-day run-in period, feasibility, safety, and tolerability outcomes will be evaluated for all the recruited patients, as outlined in the table above. Completion of ≥80% of RIC sessions, lack of significant safety concerns by the site investigator, patient willingness to proceed, and verification that the subject continues to meet all study inclusion and exclusion criteria are required to proceed to the next phase of the study including cognitive testing, activities of daily living, and randomization, followed by MRI, blood draw and provision of the patient diary.

Medical history: Intervening clinical stroke, new medical diagnoses, new surgeries, change in medications.

Physical examination: NIH Stroke Scale score, arm examination.

Print out of recorded sessions on device: The RIC device will print out the number of completed sessions. By comparing the number of recorded sessions with the total number of expected sessions, study staff will determine whether ≥80% of the expected sessions have been completed. If <80% of the expected sessions have been completed, the participant will not be randomized and subject participation will cease. If ≥80% of the expected sessions have been completed then the subject will continue with the study visit to verify that all inclusion and exclusion criteria are still met and, if appropriate, to undergo randomization and biomarker testing.

Cognitive testing**:** MoCA, plus a brief neuropsychological test battery. Test choices are based on recommendations for VCI research from the Canadian Stroke Network and National Institute of Neurological Disorders and Stroke.[54] Performed by a blinded neurologist, neuropsychologist, trained cognitive clinic nurse, or trained study staff.

| Domain | Name | Time (min) |
|---|---|---|
| Processing speed | Trail-Making Part A[43] | 3 |
| Executive | Trail Making Part B[43] | 5 |
| | Controlled Oral Word Association[55,56] | 4 |
| Memory | CERAD 10-item word list learning [57] | 6 |

| | | |
|---|---|---|
| | | Total 18-20 minutes |

Neuropsychiatric symptoms: Mild Behavioural Impairment Tracking Tool (MBI Tracking Toolchecklist) will be completed by the informant. The MBI Tracking Tool is based on the validated Mild Behavioural Impairment Checklist, but adapted to track changes in neurobehavioural symptoms over a span of days to weeks.

Activities of daily living: BADLS will be completed by the informant.

After the above assessments are completed, subjects who continue to meet all study inclusion and exclusion criteria according to the data collected up to this stage are then randomized to either of the two treatment arms. Following randomization, the following study procedures are carried out:

Provision of patient diary including NRS assessments for treatment-related pain and discomfort: The subject will be issued a diary that includes checkbox reminders for their daily at-home RIC sessions, as well as the Numeric Rating Score(NRS) for pain which will be recorded after every session. In the NRS, the subject will be asked to indicate, at the end of the session, with a mark the level of worst pain experienced during the entire session and the level of pain at the end of the last cycle of cuff inflation, ranging from 0 (no pain) to 10 (worst imaginable pain).

Venipuncture for blood draw: Venipuncture will be performed with withdrawal of 20 mL of blood. Blood will be frozen at -80 degrees and shipped to the University of Calgary for analysis in a central laboratory. Blood will be tested for levels of: homocysteine, circulating nitrite, interleukin 10, matrix metalloproteinases 2 and 9, TNF-alpha, interferon gamma, microRNA-144, SDF-1-alpha, and heat shock protein-27. 10 mL of blood will be stored at -80 for potential future use to explore newly emerging biomarkers of RIC response.

MRI scan: Subjects with have an MRI scan that includes the sequences in the following table. MRI sequence parameters are based on the Canadian Dementia Imaging Protocol (https://www.cdip-pcid.ca) and should the match the table below, although slight deviations to account for vendor hardware and software differences are expected to be necessary. MRI field strength will be 1.5T or 3T. MRI quality control will be ensured by: 1) requiring all sites to use a local phantom for MRI quality control according to their own practice, but at minimum adhering

to standards from the American College of Radiology[58], 2) qualification of the site for MRI scanning by review a phantom scan collected at each site, 3) review of each subsequent scan from each site for protocol adherence and quality. Sites are qualified to participate in the study via review and qualification of the phantom scan at each site by the University of Calgary Stroke Core Imaging Laboratory by a core lab-certified radiologist and MR physicist or biomedical engineer. Only sites that demonstrate the ability to acquire protocol-adherent, quality scans are allowed to participate in the trial. The scan quality control processes ensure that study MRI data are collected according to protocol specifications with sufficient quality for analysis of imaging endpoints.

**MRI Sequence Parameters**

| Sequence | TE (ms) | TR (ms) | Voxel size (mm) | Other |
|---|---|---|---|---|
| 3D T1-weighted | min | min | 1x1x1 | TI=650 ms, flip angle=9 |
| Dual echo T2/PD | Min/90 | 3300 | 0.94x0.94x3.0 | Echo train length 12 |
| FLAIR | 120 | 9000 | 0.94x0.94x3.0 | TI 2500 ms, flip angle 90 |
| SWI | 3.3 | 30 | 1x1x2 | flip angle 20 |
| DTI | min | 6000 | 2x2x2 | *b*=1000, 32 directions |
| ASL | | | 2x2x2 | PCASL |

Parameters shown are for a GE 3.0T scanner. Full parameters for all major vendors at 1.5 and 3T will be provided to sites in an MRI procedures manual. Estimated total acquisition time is 32 minutes. TE, echo time; TR, repetition time; TI, inversion time; T2, T2 relaxation time weighted; T1, T1 relaxation time weighted; FLAIR, fluid attenuated inversion recovery; DTI, diffusion tensor imaging; ASL, arterial spin label; PCASL, pseudo-continuous ASL.

**Day 1-3 telephone follow-up visit**

Within three days of randomization (days 1-3) and following at least one RIC session at home by the subject, the patient will receive a telephone call from a research nurse to discuss and potentially trouble-shoot issues with compliance or safety/tolerability.

**Day 15 telephone follow-up visit**

The day 15 telephone visit should be booked within ±2 days. The patient will receive a telephone call from a research nurse to discuss and potentially trouble-shoot issues with compliance or safety/tolerability.

**Day 30 in-person follow-up visit**

The day 30 visit should be booked within ±2 days. Patients will be instructed to use the RIC device up to the day prior to their 30-day follow-up visit. They will undergo the following assessments, all of which will be conducted and interpreted by assessors blinded to the patient's randomization:

- Medical history: Intervening clinical stroke, new medical diagnoses, new surgeries, change in medications.
- Physical examination: NIH Stroke Scale score, arm examination. Done by a blinded assessor.
- Retrieval of patient diary with VAS pain scores
- Cognitive testing: MoCA, Trails A and B, Controlled Oral Word Association, 10-item word list recall, performed by a blinded neurologist/neuropsychologist/trained cognitive clinic nurse.
- Neuropsychiatric symptoms: Mild Behavioural Impairment Tracking Tool will be completed by the informant.
- Activities of daily living: BADLS completed by the informant.
- Venous blood-draw: Blood will be obtained by venipuncture using the same protocol as for the randomization visit, frozen at -80 degrees and shipped to the University of Calgary for analysis in a central laboratory.
- MRI**:** The same protocol will be used as at the randomization visit.

**90-day in-person follow-up visit**

The day 90 visit should be booked within ±2 days. At this visit the following assessments will be done, all of which will be conducted and interpreted by assessors blinded to the patient's randomization:

- Cognitive testing: MoCA, Trails A and B, Controlled Oral Word Association, 10-item word list recall, performed by a blinded neurologist/neuropsychologist/trained cognitive clinic nurse.
- Neuropsychiatric symptoms: Mild Behavioural Impairment Tracking Tool will be completed by the informant.
- BADLS completed by the informant.

- Venous blood-draw: Blood will be obtained by venipuncture using the same protocol as for the randomization visit, frozen at -80 degrees and shipped to the University of Calgary for analysis in a central laboratory.
- MRI**:** The same protocol will be used as at the randomization visit.

**Exit Interview**

Near study close out, participants and their care partners at the Calgary study site will be invited to participate in an exit interview in a group setting regarding their experiences in the trial. We will aim to include 4-6 participants with their care partners. Research staff will lead a qualitative, semi-structured interview designed to elicit information on the participant's experiences within the trial including the ease of use of the RIC device, the quality of the user manual and other patient instructions, the tolerability of the treatment, and advice for conduct of future trials.

UNIVERSITY OF CALGARY
Healthy Brain Aging Labs
University of Calgary/Foothills Medical Centre
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# CONSENT FORM

**TITLE:** **Trial of Remote Ischemic Pre-Conditioning in Vascular Cognitive Impairment (TRIC-VCI)**

**SPONSOR:** Canadian Institutes of Health Research

**Site Principal Investigator: Dr. Eric Smith**
**403-210-7611**

**Co-Investigators**: Dr. Philip Barber, Dr. Zahinoor Ismail

This consent form, a copy of which has been given to you, is only part of the process of informed consent. It should give you the basic idea of what the research is about and what your participation involves. If you want more details about something mentioned here, or something not addressed, you should feel free to ask. Please take the time to read this carefully and to understand any accompanying information.

## BACKGROUND

You are being asked to consider participating in this study because you have a condition called mild Vascular Cognitive Impairment (also known as vascular mild neurocognitive disorder). In this condition, you or the people close to you have noticed changes in your cognition (memory, processing, or reasoning ability) and there is evidence on a brain scan that it is probably due to little strokes or low brain blood flow.

Remote ischemic conditioning (RIC) is a technique to increase blood flow to the brain. It is intended to be performed daily by patients at home. Each session consists of inflating a blood-pressure cuff around an arm to a pressure sufficient to reduce blood flow to the arm for 5 minutes after which it is kept deflated for 5 minutes to restore normal blood flow. This is repeated four times in each treatment. Inducing this brief period of cut off of blood flow ("ischemia") in an organ (the arm) that is far away ("remote") from the brain, may "condition" the brain to increase blood flow and make the brain less vulnerable to problems like new little strokes.

There are no treatments for mild vascular cognitive impairment that are approved by Health Canada. We are testing different regimens of RIC to see how well this treatment can be implemented by patients. This is the first step in a program intended to see if RIC will be an effective treatment for mild vascular cognitive impairment. Thousands of patients have undergone RIC as part of other research studies, and no major harmful effects have been reported.

## WHAT IS THE PURPOSE OF THE STUDY?

The purpose of this study is to determine whether RIC performed once a day on one arm or twice a day on one arm can be implemented successfully by patients, and whether it will improve cognition, brain imaging and blood markers.

## WHAT WOULD I HAVE TO DO?

You will be asked to attend an **initial screening visit** to assess your eligibility for the trial and receive instruction on how to use the RIC device. You will be asked to attend the visit with a **study partner** – someone who knows you well and may be helping you at home. This person will be asked to complete some forms at the screening visit and each in-person visit thereafter, to gather important information about how you are doing that you may not have noticed yourself. Your study partner will also be asked to provide written consent for their role in this study.

At the screening visit, you will be asked to perform RIC therapy once daily, in one arm, for a total of at least 14 days (**"run-in" period**). This will be followed by a telephone follow-up visit at 1- to 3-days after beginning the run-in period, when you will be asked about any issues or concerns, and to provide further education on how to use the device. Another in-person clinic visit may be scheduled, at the discretion of the site investigator, if further training and education are needed.

The RIC procedure is performed by a blood pressure machine that will inflate the blood pressure cuff to a high pressure, stay at that pressure for 5 minutes, and then deflate. It is normal to have some tingling or discomfort in the arm when the cuff is inflated, but it should go away soon after the cuff deflates. The device records and documents each RIC cycle. You can stop the RIC process at any time if you experience any major discomfort. However, you will be required to tolerate the treatment and demonstrate completion of **at least 12 of 14 treatment sessions** to proceed to the next part of the trial, the randomization visit.

You will be given a **study diary** that includes checkbox reminders for your daily at-home RIC sessions, as well as a scale for pain and discomfort, if you experience any (Visual Analogue Scale). In this scale, you will be asked to mark, at the end of the session, the level of worst discomfort experienced during the entire session and the level of discomfort at the end of the last cycle of cuff inflation, ranging from 0 (no discomfort) to 10 (worst imaginable pain). We expect that most patients will tolerate the RIC sessions.

At the randomization visit, you will be randomly (by chance) placed in one of two groups –

1. RIC once a day on one arm
2. RIC twice a day on one arm

Neither you, the study staff nor the investigator(s) can decide which group you are in. You will have a roughly 50% chance of being placed in either group. You will know which group you are in, but the study clinicians who assess you later to see how things have changed or progressed, will not know which group you are in.

You will be asked to perform RIC as assigned, every day for 30 days. A telephone follow-up visit will be done 1-3 days after randomization, and at 15 days, to help address any issues or concerns with the treatment.

You will stop the assigned treatment on day 30 after randomization, at which point you will be invited to an in-person follow-up visit. A final follow-up in-person visit will occur at 3-months after randomization (2 months free of RIC).

## Procedures

### MRI Scans:

An MRI (magnetic resonance imaging) is an electronic picture of your brain created using a strong magnet instead of x-rays.

Each MRI will take approximately 1 hour to complete. You will lie on your back and enter the MR machine for the study, during which time you will hear loud knocking noises. Other than loud noise, this is a painless and safe procedure. You will be asked to wear hearing protection in the form of earplugs. People with pacemakers, aneurysm clips, cochlear implants, or metal/foreign objects in their eyes are not permitted to undergo MR studies.

There are 3 MRI scans involved in this study – one around the time of the randomization visit, one at 30-days, and one at 90-days.

### Blood Sample Collection:

At the randomization visit and at 30-days and 90-days after randomization, a blood sample (slightly more than 1 tablespoon) will be collected. The blood will be tested in a University of Calgary laboratory for levels of various proteins and nucleic acids that are already thought to be relevant markers of changes in the body with RIC therapy. About half of each blood sample will be stored at -80 degrees Celsius for potential future use to explore new markers of RIC response.

### Cognitive Assessments of Memory and Thinking Skills:

A qualified member of the study staff will administer paper and pencil tests to assess your memory and thinking skills. These assessments will take about 1 hour to complete. Breaks will be allowed if needed.

## HOW MANY PEOPLE WILL TAKE PART IN THIS STUDY?

We plan to include 24 people in this study at approximately five centres within Canada. About 8 people will participate in this study at the University of Calgary. The length of this study for participants is 3.5 months (including the run-in period). The entire study will run for about one year.

## WHAT ARE THE RESPONSIBILITIES OF STUDY PARTICIPANTS?

If you decide to participate in the study, you will be asked to do the following:

- Use the study device in one arm, once daily for 14 days during the “run-in” period.
- Then after the randomization visit, use the study device **as instructed** for 30 days.
- Complete the study diary with Visual Analogue Scale scores for each RIC session.
- Answer questions about your health, your medication history and medications you take
- Complete activities to assess your memory, mood and thinking.
- Have a physical examination at in-person study visits.
- Have your blood taken at the randomization visit, at 30-days, and at 90-days (end of study).

- Have an MRI (magnetic resonance imaging) brain scan done at the randomization visit, at 30-days, and at 90-days after randomization.
- Participate according to the study visit schedule as explained below.

**Screening visit:**
The assessments performed at this visit will determine if you are eligible to participate in the study. The screening visit should take approximately 3 hours to complete. Prior to starting we will review this consent form with you and answer any questions that you may have. If you agree to participate, you will have the following assessments done:

- Review of your health history and medications.
- Physical exam including blood pressure assessment, brief neurological examination, and examination of your arms
- Cognitive assessments and mood assessments. A qualified member of the study staff will administer paper and pencil tests to assess your memory and thinking skills. Breaks will be allowed if needed.
- Your study partner will be asked to complete some questionnaires about your cognition and how you are functioning in your daily life. If your study partner does not attend this appointment, then they will be contacted by telephone or post.
- Any brain CT or MRI scans done within the last year will be reviewed for study eligibility.
- You will be given a study diary that includes checkbox reminders for your daily at-home RIC sessions, as well as a pain scale (Visual Analogue Scale) as described above.

If you meet the criteria for the study, you will be invited to participate in the 14-day minimum run-in period. A blood sample will be collected. You will be taught how to use the RIC and will be observed performing a full session (4 cycles of ischemia-reperfusion) to ensure that you are using the device correctly, before being sent home with the device.

**Telephone follow-up**

You will be contacted by telephone in 1-3 days after the screening visit, when you will be asked about any issues or concerns, and to provide further education on how to use the device. Another in-person clinic visit may be scheduled, at the discretion of the site investigator, if further training and education are needed.

**Randomization visit**

This will happen a minimum of 14 days after the screening visit. It will take about 90 minutes. You will have the following assessment done:

- Review of your health history and medications.
- Physical exam including brief neurological examination and examination of your arms
- Review print-out of recorded sessions on the RIC device
- Review of your study diary
- Cognitive assessments and mood assessments. A qualified member of the study staff will administer paper and pencil tests to assess your memory and thinking skills. Breaks will be allowed if needed.
- Your study partner will be asked to complete some questionnaires about your cognition and how you are functioning in your daily life.

If you complete at least 12 of 14 RIC sessions, are not found to have any safety concerns by the site investigator, are willing to proceed, and continue to meet all study inclusion and exclusion

criteria, you will proceed to the next part of the study and will be randomly (by chance) assigned to one of the three study groups. You will have the following assessments done:

- A blood sample will be collected
- MRI scan of your brain will be performed (this may be a separate appointment)

You will receive further instruction on how to use the device based on your assigned group.

### Day 1-3 telephone follow-up visit

Within three days of randomization and after you have completed at least one RIC session at home, you will receive a telephone call from a research nurse to discuss and potentially trouble-shoot issues or concerns that you may be having.

### Day 15 telephone follow-up visit

Around 15 days after the randomization visit, you will receive a second telephone call from a research nurse to discuss and potentially trouble-shoot issues or concerns that you may be having.

### Day 30 in-person follow-up visit

You will be instructed to use the RIC device up to the day prior to the 30-day follow-up visit (which will be 28-32 days after the previous visit). This visit will take about 90 minutes, plus the time for the brain scan. You will have the following assessments done **by assessors who should not know which group you have been assigned to**:

- Review of your health history and medication changes since the last visit.
- Physical exam including brief neurological examination and examination of your arms.
- Review print-out of recorded sessions on the RIC device, which you will **return** at this point
- Review of your study diary, which you will **return** at this point.
- Cognitive assessments (A qualified member of the study staff will administer paper and pencil tests to assess your memory and thinking skills) and mood assessments. Breaks will be allowed if needed.
- Your study partner will be asked to complete some questionnaires about your cognition and how you are functioning in your daily life.
- A blood sample will be collected.
- MRI scan of your brain will be performed (this may be a separate appointment).

**Please <u>do not</u> tell the assessors which group you have been assigned to, or how many times per day you are using the device.**

### 90-day follow-up visit

At 88-92 days, you will be invited back for a follow-up visit. This will take about 60 minutes. You will have the following assessments done **by assessors who should not know which group you have been assigned to**:

- Cognitive assessments (A qualified member of the study staff will administer paper and pencil tests to assess your memory and thinking skills) and mood assessments. Breaks will be allowed if needed.
- Your study partner will be asked to complete some questionnaires about your cognition and how you are functioning in your daily life.
- A blood sample will be collected

- MRI scan of your brain will be performed (this may be a separate appointment)

**Please do not tell the assessors which group you have been assigned to, and how many times you are using the device.**

## Study end visit

Near the end of the study, after all the participants have been enrolled and completed their visits, we may invite you to participate in a focus group interview with other participants and their spouses or care partners. We will ask you and the other participants questions about your experience with the RIC device. We will give you the opportunity to tell us how we can use the device better in the future. This session may last up to two hours and will be audio-recorded.

**If you need to stop using the RIC device or decide to stop participating in the study**, you will still be invited to come in and complete the assessments scheduled for the 30-day and 90-day visits before leaving the study, if possible.

## WHAT ARE THE RISKS?

You may experience side effects from participating in this study. Some side effects are known and are listed below.

### Study device risks:

Most side effects are mild or moderate and usually transient for the study device.

The following side effects have been seen in studies of RIC:

- Local pain or discomfort in the arm while the cuff is inflated
- Transient colour change, numbness, or tingling in the arm while the cuff is inflated
- A rash with some red dots where the cuff was inflating

The following side effects have **not** been observed in studies of RIC and are **not** expected to occur in this study, but could occur in theory. **If any of these side effects occur please stop RIC sessions immediately and call your study doctor:**

- Local swelling of the arm that continues well beyond the end of the RIC session
- Redness or paleness of the arm that continues well beyond the end of the RIC session
- Coldness of the arm that continues well beyond the end of the RIC session
- Tenderness or loss of sensation in the arm that continues well beyond the end of the RIC session
- Breakdown of the skin in the area where the cuff is placed
- Any other skin lesions in the area where the cuff is placed
- Chest pain or shortness of breath
- Diagnosis of Pulmonary Embolism (PE, lung clot) or Deep Vein Thrombosis (DVT, arm vein clot) by a healthcare provider

This is not a complete list of side effects. If you experience any unexpected effects during the study, you should contact study staff immediately (Do not wait for the next study visit.)

You should discuss these risks with the study doctor. Ask the study doctor if you have questions about the signs or symptoms of any side effects you read about in this consent form.

**Potential Interactions with Other Medications:** You can continue to take all you regular medications while on RIC. However, if you are on therapeutic **anticoagulation** (blood being greatly thinned with medications like warfarin, dabigatran, rivaroxaban, apixaban, heparin, enoxaparin, dalteparin) then as a precautionary measure you will not be included in the study. If you are started on therapeutic anticoagulation during the course of the study, please get in touch right away (see contact number below).

**Blood draw risks:**
The study doctor or study staff will take your blood by inserting a needle in your arm. Some problems you might have from this are:

- It may hurt.
- You may get a bruise.
- You may feel dizzy.
- You may get an infection.

**MRI risks:**
Some people may experience anxiety while they are in the scanner due to banging sounds from the machine or the small space. This is why we will ask you to wear earplugs. Some people may feel a little "closed-in" while inside the machine, but patients are able to speak with someone at all times and can stop the test at anytime. Some discomfort may arise from maintaining the same position throughout the session. You will be made as comfortable as possible using knee support, pillows, and blanket. You are free to discontinue the study, if you feel uncomfortable. There is also a risk of injury if metal is brought into the imaging room, which might be pulled into the MRI magnet. People with pacemakers, aneurysm clips, artificial heart valves, ear implants or metal/foreign objects in their eyes are not permitted to have an MRI. **Please tell the study doctor if you have any such implants.**

If there are incidental findings on your MRI that in the opinion of the study doctor may be considered clinically significant, this will be discussed with you and your family doctor, including options for further actions.

**Cognitive Assessment risks:**
The pencil and paper tests used in cognitive testing can take up to 1 hour to complete and may be tiring. You can request a break any time you feel you need one.

If the study investigator learns any new information regarding the risks involved, or any other finding or change to the study that might affect your willingness to continue in the study, you will be told about it.

## WILL I BENEFIT IF I TAKE PART?

If you agree to take part in this study, there may or may not be direct benefit to you. We hope the information learned from this study will benefit people with vascular cognitive impairment in the future.

## DO I HAVE TO PARTICIPATE?

Your participation in this study is strictly voluntary. If you decide not to participate it will not affect your other medical care in any way.

The investigators can remove you from the study at any time, even if you want to stay in the study. This could happen if:

- The study investigator believes it is best for you to stop being in the study
- You do not follow the study directions
- The sponsor stops funding the study for any reason

You can stop participating at any time. However, if you decide to stop participating in the study, we encourage you to talk to the study team. To help you leave the study safely, the study doctor may ask you to complete some tests. Your decision will be honored and will be discussed with your Substitute Decision Maker (SDM).

## WILL I BE PAID FOR PARTICIPATING, OR DO I HAVE TO PAY FOR ANYTHING?

You will not be compensated for your participation in this study. However, you and your caregiver will be reimbursed for parking expenses for each study visit.

There is no cost to you for the study visits or tests that are part of the study. In addition, you do not have to pay for RIC study device – it will be provided to you for the duration of the study. At the end of the study, you will be asked to return the device.

## WILL MY RECORDS BE KEPT PRIVATE?

Any of your personal information (information about you and your health that identifies you as an individual) collected or obtained, whether you choose to participate or not, will be kept confidential and protected to the fullest extent of the law. All personal information collected will be kept in a secure location. All computers used to hold information will be encrypted as per University of Calgary policy. The data for this study will be retained for 25 years.

You have the right to have any information about you and your health that is collected, used or disclosed for this study to be handled in a confidential manner.

If you decide to participate in this study, the investigator(s) and study staff will look at your personal health information and collect only the information they need for this study. Personal health information is health information about you that could identify you because it includes information such as your;

- name,
- address
- telephone number,
- date of birth,
- new and existing medical records, or
- the types, dates and results of various tests and procedures.

You have the right to access, review and request changes to your personal health information.

Access to your personal health information will take place under the supervision of the Principal Investigator.

“Study data" is health information about you that is collected for the study, but that does not directly identify you. Any study data about you that is sent outside of the hospital will have a code and will not contain your name or address, or any information that directly identifies you.

Your full date of birth will be included on all images (i.e. MRI scans) disclosed outside the institution for the purpose of the study.

Study data that is sent outside of the hospital will be used for the research purposes explained in this consent form. As part of a movement to more open science, researchers now share the information collected in their studies with each other. This will include your study data, but not any of your personal health information. The study data may be placed on websites such as the University of Calgary PRISM Dataverse (https://libanswers.ucalgary.ca/faq/164924).

The investigator(s), study staff and the other people listed above will keep the information they see or receive about you confidential, to the extent permitted by applicable laws. Even though the risk of identifying you from the study data is very small, it can never be completely eliminated.

The study staff, the Conjoint Health Research Ethics Board at the University of Calgary, the monitor(s), and the regulatory authority (Health Canada) will have access to your personal information for purposes associated with the study, but will only be allowed to access your records under the supervision of the Principal Investigator and will be obligated to protect your privacy and not disclose your personal information. None of your personal information will be given to anyone without your permission unless required by law. When the results of this study are published, your identity will not be disclosed. Even though the risk of identifying you from the study data is very small, it can never be completely eliminated.

Authorized representatives from the University of Calgary and the Conjoint Health Research Ethics Board may look at your identifiable medical/clinical study records held at the University of Calgary for quality assurance purposes.

When the results of this study are published, your identity will not be disclosed.

You have the right to be informed of the results of this study once the entire study is complete.

A description of this clinical trial will be available on *http://www.ClinicalTrials.gov*, as required by U.S. Law. This website will not include information that can identify you. At most, the website will include a summary of the results of all participants. You can search this website at any time.

## IF I SUFFER A RESEARCH-RELATED INJURY, WILL I BE COMPENSATED?

You may contact the individuals listed at the beginning of this consent form at any time for treatment of side effects, questions, emergencies or FOR ANY OTHER REASON. In the event that you suffer injury as a result of participating in this research, no compensation will be provided to you by the University of Calgary, Alberta Health Services or the Researchers. Nonetheless, you still have all your legal rights. Nothing said in this consent form alters your right to seek damages.

All participants in a research study have the following rights:

1. You have the right to have this form and all information concerning this study explained to you and if you wish translated into your preferred language.

2. Participating in this study is your choice *(voluntary)*. You have the right to refuse to participate, or to stop participating in this study at any time without having to provide a reason. If you choose to withdraw, it will not have any effect on your future medical treatment or health care. Should you choose to withdraw from the study you are encouraged to contact individuals listed at the beginning of this consent form.

3. You have the right to receive all significant information that could help you make a decision about participating in this study. You also have the right to ask questions about this study and your rights as a research participant, and to have them answered to your satisfaction, before you make any decision. You also have the right to ask questions and to receive answers throughout this study. If you have any questions about this study you may contact the person in charge of this study at your centre (Principal Investigator), Dr. Eric Smith at 403-944-1594.

4. By signing this consent form, you do not give up any of your legal rights.

5. You have the right to receive a copy of this signed and dated informed consent package before participating in this study.

6. You have the right to be told about any new information that might reasonably affect your willingness to continue to participate in this study as soon as the information becomes available to the study staff. This may include new information about the risks and benefits of being a participant in this study.

7. If you become sick or injured as a direct result of your participation in this study, your medical care will be provided. Please contact the study doctor if you feel you have been injured as a result of this study.

8. If, as a result of your participation in this study, any new clinically important medical information about your health is obtained, you will be given the opportunity to decide whether you wish to be made aware of that information.

9. You have the right to access, review and request changes to your personal information (i.e. address, date of birth).

10. You have the right to be informed of the results of this study once the entire study is complete.

11. For medical emergencies, proceed to the emergency room of the nearest hospital and contact study personnel as soon as possible. All adverse events should be reported to Dr. Eric Smith at 403-944-1594 as soon as possible. **In case of an adverse event or to reach the study physician for urgent matters, please contact the Foothills Hospital locating number 403-944-1110 and ask for Dr. Eric Smith to be paged. This is a 24-hour emergency contact number.**

# SIGNATURES

*The role of the caregiver as the participant's study partner is explained on pages 15 and 16 of the consent form, and the caregiver will separately consent to these duties on page 16.*

## Participant

By signing this form, I confirm that:

- This research study has been fully explained to me and all of my questions answered to my satisfaction
- I understand the requirements of participating in this research study
- I have been informed of the risks and benefits, if any, of participating in this research study
- I have been informed of any alternatives to participating in this research study
- I have been informed of the rights of research participants
- I have read each page of this form
- I authorize access to my personal health information (medical record) and research study data as explained in this form
- I have agreed to participate in this study or agree to allow the person I am responsible for to participate in this study

Your signature on this form indicates that you have understood the information regarding your participation in the research project and agree to participate as a subject. In no way does this waive your legal rights nor release the investigators, or involved institutions from their legal and professional responsibilities. You are free to withdraw from the study without jeopardizing your health care. You may withdraw from the study at any time, without need to provide a reason, by contacting the Principal Investigator Dr. Eric Smith. Samples and data may be withdrawn up until the point that they are accessed by external researchers. Once coded samples or data are sent to approved researchers, they can no longer be withdrawn from the study.

If you have further questions concerning matters related to this research, please contact the Principal Investigator, Dr. Eric Smith at (403) 944-1594 or (403) 210-7611.

If you have any questions concerning your rights as a possible participant in this research, please contact the Chair, Conjoint Health Research Ethics Board, University of Calgary at 403-220-7990.

| Participant's Name | Signature | Date (*DD/MMM/YY*) |
|---|---|---|
| Investigator Name | Signature | Date (*DD/MMM/YY*) |
| Witness' Name | Signature | Date (*DD/MMM/YY*) |

The University of Calgary Conjoint Health Research Ethics Board has approved this research study.

A signed copy of this consent form has been given to you to keep for your records and reference.

## STUDY PARTNER INFORMATION

I understand that _____, a patient with vascular cognitive impairment whom I know well and for whom I am/will be a caregiver, has consented to be a research subject in the TRIC-VCI study. This study is examining whether different doses or schedules of Remote Ischemic pre-Conditioning have any advantage over each in other slowing cognitive or brain changes in patients with vascular cognitive impairment. I have read and understand the consent form that he/she has signed. I understand that in order for this study to be conducted in the most valuable manner possible, I will have the following responsibilities during the time that the patient remains in this study:

1. I will accompany the patient to all clinic visits.

2. I will ensure that the patient keeps all study appointments (phone or in-person) as listed in the schedule that I will receive. I will provide information about how the patient is doing when I bring him/her in for clinic visits and complete the necessary caregiver/informant questionnaires, and provide information if I'm contacted by telephone as per the predefined schedule.

3. If any severe, serious, or unexpected event occurs to the patient between clinic visits, I will immediately call the Study Doctor or his/her representative to report it, whether or not I or the patient thinks that it might be due to the study treatment. I will follow all instructions the Study Doctor or his/her representative gives me at that time.

If for any reason I become unable to fulfill these responsibilities, I will notify the Study Doctor immediately. I understand that I may be asked to find someone else to take over these responsibilities for whatever time I am unavailable. If this is not possible, I understand that it might be necessary to discontinue the patient's participation in the study.

For this study, I am aware that the study physician will need to document in the patient's chart that I am his/her study partner/caregiver, and certain information will be collected from me such as my contact information.

I am also aware that the information collected as part of this study will be kept confidential unless release is required by law, and only used for the purpose of the research study as stated in the study objectives above.

## DOCUMENTATION OF STUDY PARTNER CONSENT

I have read this document/had its contents explained to me and understand the purpose of this study and what the participation of the patient for whom I provide care will involve. I agree to assist the patient in the study for the entire duration of the trial and to attend the visits as required.

| _____ | _____ | _____ |
|---|---|---|
| Caregiver's Name | Signature | Date (*DD/MM/YY*) |

The University of Calgary Conjoint Health Research Ethics Board has approved this research study.
A signed copy of this consent form has been given to you to keep for your records and reference.

CRU #044 TRIC VCI Plate #001 Screening

**Subject ID:** Centre Subject ID **Date:** yyyy mm dd

## SCREENING *(page 1 of 6)*

| | |
|---|---|
| Has the research candidate and their study partner given informed consent and signed the consent forms? | ☐ Yes ☐ No |

| INCLUSION CRITERIA: All responses must be YES to qualify: | | |
|---|---|---|
| Criterion | Operationalized as: | Determination |
| Age 60-85 | N/A | ☐ Yes ☐ No |
| Independent with basic activities | BADLS question 2 response a) selected | ☐ Yes ☐ No |
| | BADLS question 4 response a) selected | ☐ Yes ☐ No |
| | BADLS question 5 response a) selected | ☐ Yes ☐ No |
| | BADLS question 6 response a) selected | ☐ Yes ☐ No |
| | BADLS question 7 response a) selected | ☐ Yes ☐ No |
| | BADLS question 8 response a) selected | ☐ Yes ☐ No |
| | BADLS question 9 response a) selected | ☐ Yes ☐ No |
| | BADLS question 14 response a) selected | ☐ Yes ☐ No |
| Cognitive impairment | MoCA total score 24 or lower | ☐ Yes ☐ No |
| Cognitive concern | EITHER 2 or more positive responses on AD8<br>OR<br>Clinician judgement based on history | ☐ Yes ☐ No |
| Evidence of cerebral small vessel disease | EITHER 2 or more supratentorial subcortical infarcts<br>OR<br>Beginning confluent or confluent WMH on modified AR-WMC scale on CT or MRI | ☐ Yes ☐ No |

CRU #044 TRIC VCI Plate #002 Screening

**Subject ID:** ☐☐ ☐☐☐ (Centre / Subject ID) **Date:** ☐☐☐☐ ☐☐ ☐☐ (yyyy / mm / dd)

## SCREENING *(page 2 of 6)*

| EXCLUSION CRITERIA: All responses must be NO to qualify: | |
|---|---|
| **Criterion** | **Determination** |
| Large cortical infarcts (>10mm) | ☐ Yes ☐ No |
| Neuroimaging evidence of mass lesion, intracerebral hemorrhage, vascular malformation, or evidence non-vascular disease such as hydrocephalus | ☐ Yes ☐ No |
| Resides in a long term care facility | ☐ Yes ☐ No |
| Other significant neurological or psychiatric disease (e.g. multiple sclerosis) | ☐ Yes ☐ No |
| Subject does not have a study partner who can provide corroborative information | ☐ Yes ☐ No |
| English or French is not sufficiently proficient for clinical assessment and neuropsychological testing | ☐ Yes ☐ No |
| Total score on the MoCA 12 or lower | ☐ Yes ☐ No |
| Unable to undergo MRI due to medical contraindications such a cardiac pacemaker, or inability to tolerate the procedure | ☐ Yes ☐ No |
| Co-morbid medical illness that in the judgment of the study investigator makes it unlikely that the participant will be able to complete one year of study follow-up | ☐ Yes ☐ No |
| On therapeutic anticoagulation with doses used for treatment of deep venous thrombosis, pulmonary embolism, or for stroke prevention in atrial fibrillation | ☐ Yes ☐ No |
| Significant bleeding diathesis | ☐ Yes ☐ No |
| Any symptomatic or previously known arm soft-tissue disease, vascular injury, or peripheral vascular disease (PVD) | ☐ Yes ☐ No |
| Hypertension with systolic blood pressure >=180 mmHg despite medical treatment at the time of enrolment | ☐ Yes ☐ No |
| Planned revascularization (any angioplasty or vascular surgery) within the next 3 months | ☐ Yes ☐ No |
| Planned surgical procedure within the next 3 months | ☐ Yes ☐ No |
| Currently receiving an investigational drug or device by other studies | ☐ Yes ☐ No |

*Signature of investigator confirms the Inclusion/Exclusion Criteria :* _____

***e-signature***
***iDataFax use only***

☐☐ : ☐☐ ☐☐☐☐ ☐☐ ☐☐ (hh : mm yyyy mm dd)

PI's printed first and last name: _____

CRU #044 TRIC VCI Plate #003 Screening

**Subject ID:** ☐☐ ☐☐☐ *Centre* *Subject ID*

**Date:** ☐☐☐☐ ☐☐ ☐☐ *yyyy* *mm* *dd*

## SCREENING *(page 3 of 6)*

| DEMOGRAPHICS | |
|---|---|
| 1. Age: | ☐☐ |
| 2. Sex: | ☐ Male ☐ Female |
| 3. Mother tongue (first language learned): | ☐ English ☐ French<br>☐ Other: _____ |
| 4. Marital Status: | ☐ Single ☐ Separated<br>☐ Married ☐ Divorced<br>☐ Common-law partnership ☐ Widowed |
| 5. Current living circumstance: | ☐ House or apartment/condominium that you own<br>☐ Apartment/condominium or house that you rent<br>☐ Retirement home (autonomous living)<br>☐ Residence for semi-autonomous individuals<br>☐ Nursing home or long-term care (assisted living)<br>☐ Other, please specify: _____ |
| 6. What is the highest grade or level of school completed or highest degree obtained: | ☐ Never attended school ☐ Technical school or community college<br>☐ Some primary/grade school ☐ CEGEP<br>☐ Completed primary/grade school ☐ Undergraduate degree at university (e.g., B.A, B.SC, B.Eng., LL.B., B.Ed., etc)<br>☐ Some high school<br>☐ Completed high school ☐ Some graduate (post-undergraduate) school<br>☐ Apprenticeship ☐ Graduate degree at university |

CRU #044 TRIC VCI Plate #004 Screening

**Subject ID:** Centre Subject ID **Date:** yyyy mm dd

## SCREENING *(page 4 of 6)*

| DEMOGRAPHICS | |
|---|---|
| 7. Study informant relationship to patient: | ☐ Spouse ☐ Child ☐ Parent ☐ Friend ☐ Other: _____ |
| 8. Informant frequency of contact with patient: | ☐ Daily ☐ One or more times per week ☐ One or more times per month ☐ Less than once per month |

CRU #044 TRIC VCI Plate #005 Screening

**Subject ID:** Centre Subject ID **Date:** yyyy mm dd

## SCREENING *(page 5 of 6)*

| MEDICAL HISTORY | |
|---|---|
| 1. History of prior transient ischemic attack: | ☐ Yes ☐ No |
| If yes, then complete 1.a. and 1.b. | |
| 1.a. Is there a history of more than one prior transient ischemic attack? | ☐ Yes ☐ No |
| 1.b. What was the month and year of the most recent prior transient attack? | yyyy mm |
| 2. History of prior stroke: | ☐ Yes ☐ No |
| If yes, then complete 2.a and 2.b. | |
| 2.a. Is there a history of more than one prior stroke? | ☐ Yes ☐ No |
| 2.b. What was the month and year of the most recent prior stroke? | yyyy mm |
| 3. History of carotid stenosis: | ☐ Yes ☐ No |
| 4. History of prior carotid revascularization: | ☐ Yes ☐ No |
| 4.a. Side of carotid revascularization: | ☐ R ☐ L ☐ Both |
| 5. History of hypertension or use of antihypertensive medications to control blood pressure: | ☐ Yes ☐ No |
| 6. History of diabetes mellitus: | ☐ Yes ☐ No |
| 7. History of dyslipidemia or use of antilipid medications: | ☐ Yes ☐ No |
| 8. History of myocardial infarction: | ☐ Yes ☐ No |
| 9. History of angina: | ☐ Yes ☐ No |
| 10. History of atrial fibrillation: | ☐ Yes ☐ No |
| 11. History of heart failure: | ☐ Yes ☐ No |

CRU #044 TRIC VCI Plate #006 Screening

**Subject ID:** [ ][ ] [ ][ ][ ] *Centre* *Subject ID*

**Date:** [ ][ ][ ][ ] [ ][ ] [ ][ ] *yyyy* *mm* *dd*

## SCREENING *(page 6 of 6)*

| MEDICAL HISTORY | | |
|---|---|---|
| 12. History of peripheral vascular disease: | ☐ Yes | ☐ No |
| 13. History of prior deep venous thrombosis: | ☐ Yes | ☐ No |
| 14. History of prior cancer: | ☐ Yes | ☐ No |
| 15. History of any other central nervous system diseases (list): _____ _____ | | |

CRU #044 TRIC VCI Plate #007

☐ Screening ☐ Randomization

☐ Follow Up ☐ End

**Subject ID:** ☐☐ ☐☐☐ (Centre / Subject ID)

**Date:** ☐☐☐☐ ☐☐ ☐☐ (yyyy / mm / dd)

# MEDICATIONS

| | |
|---|---|
| 1. Is the patient taking an antiplatelet drug? | ☐ Yes ☐ No |
| If yes, please answer 1.a. below: | |
| 1.a. Antiplatelet drug class(es)—select all that apply: ☐ Acetylsalicylic acid (e.g. Aspirin) ☐ Clopidogrel (Plavix) ☐ Aggrenox ☐ Persantine ☐ Ticagrelor (Brilinta) ☐ Prasugrel (Effient) | |
| 2. Is the patient taking an anticoagulant drug? | ☐ Yes ☐ No |
| 2.a. If yes, is the drug taken at doses used for treatment of deep venous thrombosis, pulmonary embolism, or for stroke prevention in atrial fibrillation? | ☐ Yes ☐ No |

3. For all other medications, please complete “Medications List” form(s).

Signature: _____ Date: ☐☐☐☐ ☐☐ ☐☐ (yyyy / mm / dd)

CRU #044 TRIC VCI Plate #008

☐ Screening ☐ Randomization ☐ Follow Up

**Subject ID:** ☐☐ ☐☐☐ (Centre / Subject ID) **Date:** ☐☐☐☐ ☐☐ ☐☐ (yyyy / mm / dd)

# PHYSICAL EXAMINATION

| PHYSICAL MEASUREMENTS MUST BE PERFORMED BY STUDY PERSONNEL BLINDED TO TREATMENT ASSIGNMENT | | | |
|---|---|---|---|
| 1. Blood pressure (seated) | | | |
| 1.a. Right arm systolic blood pressure: ☐☐☐ **mmHg** | | 1.c. Left arm systolic blood pressure: ☐☐☐ **mmHg** | |
| 1.b. Right arm diastolic blood pressure: ☐☐☐ **mmHg** | | 1.d. Left arm diastolic blood pressure: ☐☐☐ **mmHg** | |

| 2. Arm examination: | | | | |
|---|---|---|---|---|
| | RIGHT | | LEFT | |
| Radial pulse palpable | ☐ Yes | ☐ No | ☐ Yes | ☐ No |
| Ulnar pulse palpable | ☐ Yes | ☐ No | ☐ Yes | ☐ No |
| Brachial pulse palpable | ☐ Yes | ☐ No | ☐ Yes | ☐ No |
| Local edema | ☐ Yes | ☐ No | ☐ Yes | ☐ No |
| Skin breakdown | ☐ Yes | ☐ No | ☐ Yes | ☐ No |
| Rash | ☐ Yes | ☐ No | ☐ Yes | ☐ No |
| Petechiae | ☐ Yes | ☐ No | ☐ Yes | ☐ No |
| Upper arm tenderness | ☐ Yes | ☐ No | ☐ Yes | ☐ No |
| Lower arm tenderness | ☐ Yes | ☐ No | ☐ Yes | ☐ No |

| 3. Arm examination comments: |
|---|
| _____ |
| _____ |
| _____ |

| 4. Examiner blinded to treatment arm: | ☐ Yes | ☐ No |
|---|---|---|

Signature: _____ Date: ☐☐☐☐ ☐☐ ☐☐ (yyyy / mm / dd)

CRU #044 TRIC VCI Plate #009

☐ Screening ☐ Randomization

☐ Follow Up ☐ End

**Subject ID:** ☐☐ ☐☐☐ *Centre* *Subject ID*

**Date:** ☐☐☐☐ ☐☐ ☐☐ *yyyy* *mm* *dd*

## NIH STROKE SCALE *(page 1 of 3)*

| | | |
|---|---|---|
| 1a. Level of Consciousness | ☐ | 0 - Alert |
| | ☐ | 1 - Not alert, but arousable with minimal stimulation |
| | ☐ | 2 - Not alert, requires repeated stimulation to attend |
| | ☐ | 3 - Coma |
| 1b. LOC Questions *Ask patient the month and their age* | ☐ | 0 - Answers both correctly |
| | ☐ | 1 - Answers one correctly |
| | ☐ | 2 - Both incorrect |
| 1c. LOC Commands *Ask patient to open/close eyes and form/release fist* | ☐ | 0 - Obeys both correctly |
| | ☐ | 1 - Obeys one correctly |
| | ☐ | 2 - Both incorrect |
| 2. Best Gaze *Only horizontal eye movement* | ☐ | 0 - Normal |
| | ☐ | 1 - Partial gaze palsy |
| | ☐ | 2 - Forced gaze palsy |
| 3. Visual Field Testing | ☐ | 0 - No visual field loss |
| | ☐ | 1 - Partial hemianopia |
| | ☐ | 2 - Complete hemianopia |
| | ☐ | 3 - Bilateral hemianopia (blind, incl. Cortical blindness) |
| 4. Facial Palsy *Ask patient to show teeth or raise eyebrows and close eyes tightly* | ☐ | 0 - Normal symmetrical movement |
| | ☐ | 1 - Minor paralysis (flattened nasolabial fold, asymmetry on smiling) |
| | ☐ | 2 - Partial paralysis (total or near total paralysis of lower face) |
| | ☐ | 3 - Complete paralysis of one or both sides (absence of facial movement in the upper and lower face) |

CRU #044 TRIC VCI Plate #010

☐ Screening ☐ Randomization
☐ Follow Up ☐ End

**Subject ID:** ☐☐ ☐☐☐ (Centre / Subject ID) **Date:** ☐☐☐☐ ☐☐ ☐☐ (yyyy / mm / dd)

## NIH STROKE SCALE *(page 2 of 3)*

| | L | R | |
|---|---|---|---|
| 5. Motor Function Arm | ☐ | ☐ | 0 - Normal (extends arm 90º or 45º for 10 sec without drift) |
| | ☐ | ☐ | 1 - Drift |
| | ☐ | ☐ | 2 - Some effort against gravity |
| | ☐ | ☐ | 3 - No effort against gravity |
| | ☐ | ☐ | 4 - No movement |
| | ☐ | ☐ | 9 - Untestable (Joint fused/limb amputated) (*do not add score*) |

| | L | R | |
|---|---|---|---|
| 6. Motor Function Leg | ☐ | ☐ | 0 - Normal (holds leg in 30º position for 5 sec without drift) |
| | ☐ | ☐ | 1 - Drift |
| | ☐ | ☐ | 2 - Some effort against gravity |
| | ☐ | ☐ | 3 - No effort against gravity |
| | ☐ | ☐ | 4 - No movement |
| | ☐ | ☐ | 9 - Untestable (Joint fused/limb amputated) (*do not add score*) |

| | | |
|---|---|---|
| 7. Limb ataxia | ☐ | 0 - No ataxia |
| | ☐ | 1 - Present in one limb |
| | ☐ | 2 - Present in two limbs |

| | | |
|---|---|---|
| 8. Sensory *Use pinprick to test arms, legs, trunk and face, compare side to side* | ☐ | 0 - Normal |
| | ☐ | 1 - Mild to moderate decrease in sensation |
| | ☐ | 2 - Severe to total sensory loss |

| | | |
|---|---|---|
| 9. Best Language *Ask patient to describe picture, name items* | ☐ | 0 - No aphasia |
| | ☐ | 1 - Mild to moderate aphasia |
| | ☐ | 2 - Severe aphasia |
| | ☐ | 3 - Mute |

CRU #044 TRIC VCI Plate #011

☐ Screening ☐ Randomization

☐ Follow Up ☐ End

**Subject ID:** ☐☐ ☐☐☐ (Centre / Subject ID)

**Date:** ☐☐☐☐ ☐☐ ☐☐ (yyyy / mm / dd)

## NIH STROKE SCALE *(page 3 of 3)*

| | | |
|---|---|---|
| I0. Dysarthria<br>*Ask patient to read several words* | ☐ | 0 - No aphasia |
| | ☐ | 1 - Mild to moderate slurring of words |
| | ☐ | 2 - Near unintelligible or unable to speak |
| | ☐ | 9 - Intubated or other physical barrier (*do not add score*) |

| | | |
|---|---|---|
| 11. Extinction and Inattention<br>*Use visual double stimulation or sensory double stimulation* | ☐ | 0 - Normal |
| | ☐ | 1 - Inattention or extinction to bilateral simultaneous stimulation in one of the sensory modalities |
| | ☐ | 2 - Hemi-inattention, severe or to more than one modality |

Auto-Calculated Total Score Only: ☐☐

[range 0-42]

Signature: _____ Date: ☐☐☐☐ ☐☐ ☐☐ (yyyy / mm / dd)

CRU #044 TRIC VCI Plate #012 Screening

**Subject ID:** Centre Subject ID **Date:** yyyy mm dd

# HACHINSKI ISCHEMIC SCORE

| Characteristic | YES | NO |
|---|---|---|
| Abrupt onset | ☐ 2 | ☐ 0 |
| Stepwise deterioration | ☐ 1 | ☐ 0 |
| Fluctuating course | ☐ 2 | ☐ 0 |
| Nocturnal confusion | ☐ 1 | ☐ 0 |
| Preservation of personality | ☐ 1 | ☐ 0 |
| Depression | ☐ 1 | ☐ 0 |
| Somatic complaints | ☐ 1 | ☐ 0 |
| Emotional lability | ☐ 1 | ☐ 0 |
| History of hypertension | ☐ 1 | ☐ 0 |
| History of stroke | ☐ 2 | ☐ 0 |
| Associated atherosclerosis | ☐ 1 | ☐ 0 |
| Focal neurological symptoms | ☐ 2 | ☐ 0 |
| Focal neurological signs | ☐ 2 | ☐ 0 |

Auto-Calculated Total Score Only: ☐☐ [range 0-18]

Signature: _____ Date: yyyy mm dd

CRU #044 TRIC VCI Plate #013

☐ Screening ☐ Randomization

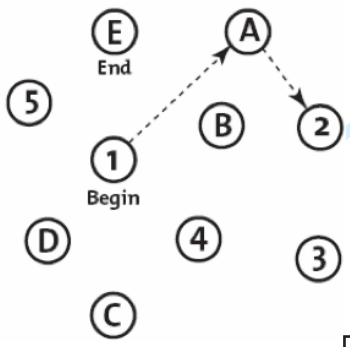
☐ Follow Up ☐ End

**Subject ID:** ☐☐ ☐☐☐ (Centre / Subject ID)

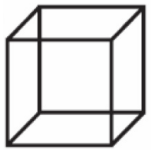
**Date:** ☐☐☐☐ ☐☐ ☐☐ (yyyy / mm / dd)

# MONTREAL COGNITIVE ASSESSMENT *(page 1 of 2)*

## VISUOSPATIAL / EXECUTIVE




☐



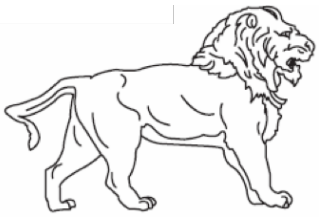

☐

Draw CLOCK (Ten past eleven)
(3 points)

☐ Contour ☐ Numbers ☐ Hands

**POINTS** ☐ /5

## NAMING



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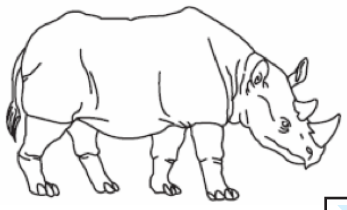

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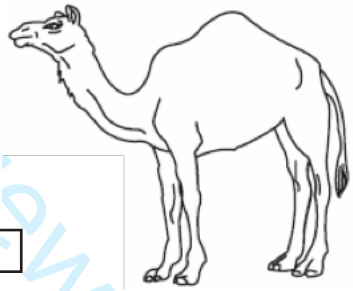

☐

**POINTS** ☐ /3

## MEMORY

Read list of words, subject must repeat them. Do 2 trials. Do a recall after 5 minutes.

| | FACE | VELVET | CHURCH | DAISY | RED |
|---|---|---|---|---|---|
| 1st trial | ☐ | ☐ | ☐ | ☐ | ☐ |
| 2nd trial | ☐ | ☐ | ☐ | ☐ | ☐ |

No Points

## ATTENTION

Read list of digits (1 digit/sec).

Subject has to repeat them in the forward order ☐ 2 1 8 5 4

Subject has to repeat them in the backward order ☐ 7 4 2

**POINTS** ☐ /2

Read list of letters. The subject must tap with his hand at each letter A. No points if ≥ 2 errors

☐ F B A C M N A A J K L B A F A K D E A A A J A M O F A A B

**POINTS** ☐ /1

Serial 7 subtraction starting at 100 ☐ 93 ☐ 86 ☐ 79 ☐ 72 ☐ 65

4 or 5 correct subtractions: **3 pts**, 2 or 3 correct: **2 pts**, 1 correct: **1 pt**, 0 correct: **0 pt**

**POINTS** ☐ /3

CRU #044 TRIC VCI Plate #014

☐ Screening ☐ Randomization
☐ Follow Up ☐ End

**Subject ID:** ☐☐ ☐☐☐ *Centre* *Subject ID*

**Date:** ☐☐☐☐ ☐☐ ☐☐ *y y y y* *m m* *d d*

# MONTREAL COGNITIVE ASSESSMENT *(page 2 of 2)*

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| LANGUAGE | Repeat: I only know that John is the one to help today. ☐<br>The cat always hid under the couch when dogs were in the room ☐ | | | | | | | ☐ /2 |
| Fluency / Name maximum number of words in one minute that begin with the letter F ☐ _____ (N ≥ 11 words) | | | | | | | | ☐ /1 |
| ABSTRACTION | Similarity between e.g. banana - orange = fruit ☐ train - bicycle ☐ watch - ruler | | | | | | | ☐ /2 |
| DELAYED RECALL | Has to recall words WITH NO CUE | FACE ☐ | VELVET ☐ | CHURCH ☐ | DAISY ☐ | RED ☐ | Points for UNCUED recall only | ☐ /5 |
| Optional | Category cue | ☐ | ☐ | ☐ | ☐ | ☐ | | |
| | Multiple choice cue | ☐ | ☐ | ☐ | ☐ | ☐ | | |
| ORIENTATION | ☐ Date ☐ Month ☐ Year ☐ Day ☐ Place ☐ City | | | | | | | ☐ /6 |

Normal ≥ 26 / 30 **Auto-Calculated Total Only** ☐☐ /30

Administered by: _____

Signature: _____ Date: ☐☐☐☐ ☐☐ ☐☐ *y y y y* *m m* *d d*

CRU #044 TRIC VCI Plate #015

☐ Screening ☐ Randomization
☐ Follow Up ☐ End

**Subject ID:** ☐☐ ☐☐☐ (Centre / Subject ID) **Date:** ☐☐☐☐ ☐☐ ☐☐ (yyyy / mm / dd)

# INFORMANT BRISTOL ACTIVITIES OF DAILY LIVING SCALE *(page 1 of 6)*

This questionnaire is designed to reveal the everyday ability of people who have memory difficulties of one form or another.

For each activity (No. 1 - 20), statements a - e refer to a different level of ability.

Thinking of the last 2 weeks, tick the box that represents your relative's/friend's AVERAGE ability. (If in doubt about which box to tick, choose the level of ability which represents their average performance over the last 2 Weeks. Tick 'Not applicable' if your relative never did that activity when they were well).

| | | |
|---|---|---|
| 1. PREPARING FOOD | ☐ | a) Selects and prepares food as required |
| | ☐ | b) Able to prepare food if ingredients set out |
| | ☐ | c) Can prepare food if prompted step by step |
| | ☐ | d) Unable to prepare food even with prompting and supervision |
| | ☐ | e) Not applicable |
| 2. EATING | ☐ | a) Eats appropriately using correct cutlery |
| | ☐ | b) Eats appropriately if food made manageable and/or uses spoon |
| | ☐ | c) Uses fingers to eat food |
| | ☐ | d) Needs to be fed |
| | ☐ | e) Not applicable |
| 3. PREPARING DRINK | ☐ | a) Selects and prepares drinks as required |
| | ☐ | b) Can prepare drinks if ingredients left available |
| | ☐ | c) Can prepare drinks if prompted step by step |
| | ☐ | d) Unable to make a drink even with prompting and supervision |
| | ☐ | e) Not applicable |

CRU #044 TRIC VCI Plate #016

☐ Screening ☐ Randomization
☐ Follow Up ☐ End

**Subject ID:** ☐☐ ☐☐☐ (Centre / Subject ID) **Date:** ☐☐☐☐ ☐☐ ☐☐ (yyyy / mm / dd)

# INFORMANT BRISTOL ACTIVITIES OF DAILY LIVING SCALE *(page 2 of 6)*

| | | |
|---|---|---|
| 4. DRINKING | ☐ | a) Drinks appropriately |
| | ☐ | b) Drinks appropriately with aids, beaker/straw etc. |
| | ☐ | c) Does not drink appropriately even with aids but attempts to |
| | ☐ | d) Has to have drinks administered (fed) |
| | ☐ | e) Not applicable |
| 5. DRESSING | ☐ | a) Selects appropriate clothing and dresses self |
| | ☐ | b) Puts clothes on in wrong order and/or back to front and/or dirty clothing |
| | ☐ | c) Unable to dress self but moves limbs to assist |
| | ☐ | d) Unable to assist and requires total dressing |
| | ☐ | e) Not applicable |
| 6. HYGIENE | ☐ | a) Washes regularly and independently |
| | ☐ | b) Can wash self if given soap, flannel, towel, etc. |
| | ☐ | c) Can wash self if prompted and supervised |
| | ☐ | d) Unable to wash self and needs full assistance |
| | ☐ | e) Not applicable |
| 7. TEETH | ☐ | a) Cleans own teeth/dentures regularly and independently |
| | ☐ | b) Cleans teeth/dentures if given appropriate items |
| | ☐ | c) Requires some assistance, toothpaste on brush, brush to mouth etc. |
| | ☐ | d) Full assistance given |
| | ☐ | e) Not applicable |

CRU #044 TRIC VCI Plate #017

☐ Screening ☐ Randomization
☐ Follow Up ☐ End

**Subject ID:** ☐☐ ☐☐☐ (Centre / Subject ID) **Date:** ☐☐☐☐ ☐☐ ☐☐ (yyyy / mm / dd)

# INFORMANT BRISTOL ACTIVITIES OF DAILY LIVING SCALE *(page 3 of 6)*

| | | |
|---|---|---|
| 8. BATH/SHOWER | ☐ | a) Bathes regularly and independently |
| | ☐ | b) Needs bath to be drawn/shower turned on but washes independently |
| | ☐ | c) Needs supervision and prompting to wash |
| | ☐ | d) Totally dependent, needs full assistance |
| | ☐ | e) Not applicable |
| 9. TOILET/COMMODE | ☐ | a) Uses toilet appropriately when required |
| | ☐ | b) Needs to be taken to the toilet and given assistance |
| | ☐ | c) Incontinent of urine or faeces |
| | ☐ | d) Incontinent of urine and faeces |
| | ☐ | e) Not applicable |
| 10. TRANSFERS | ☐ | a) Can get in/out of chair unaided |
| | ☐ | b) Can get into a chair but needs help to get out |
| | ☐ | c) Needs help getting in and out of a chair |
| | ☐ | d) Totally dependent on being put into and lifted from chair |
| | ☐ | e) Not applicable |
| 11. MOBILITY | ☐ | a) Walks independently |
| | ☐ | b) Walks with assistance i.e. furniture, arm for support |
| | ☐ | c) Uses aids to mobilise i.e. frame, sticks etc. |
| | ☐ | d) Unable to walk |
| | ☐ | e) Not applicable |

CRU #044 TRIC VCI Plate #018

☐ Screening ☐ Randomization
☐ Follow Up ☐ End

**Subject ID:** ☐☐ ☐☐☐ (Centre / Subject ID) **Date:** ☐☐☐☐ ☐☐ ☐☐ (yyyy / mm / dd)

# INFORMANT BRISTOL ACTIVITIES OF DAILY LIVING SCALE *(page 4 of 6)*

| | | |
|---|---|---|
| 12. ORIENTATION – TIME | ☐ | a) Fully orientated to time/day/date etc. |
| | ☐ | b) Unaware of time/day etc. but seems unconcerned |
| | ☐ | c) Repeatedly asks the time/day/date |
| | ☐ | d) Mixes up night and day |
| | ☐ | e) Not applicable |
| 13. ORIENTATION – SPACE | ☐ | a) Fully orientated to surroundings |
| | ☐ | b) Orientated to familiar surroundings only |
| | ☐ | c) Gets lost in home, needs reminding where bathroom is, etc. |
| | ☐ | d) Does not recognise home as own and attempts to leave |
| | ☐ | e) Not applicable |
| 14. COMMUNICATION | ☐ | a) Able to hold appropriate conversation |
| | ☐ | b) Shows understanding and attempts to respond verbally with gestures |
| | ☐ | c) Can make self-understood but difficulty understanding others |
| | ☐ | d) Does not respond to, or communicate with others |
| | ☐ | e) Not applicable |
| 15. TELEPHONE | ☐ | a) Uses telephone appropriately, including obtaining correct number |
| | ☐ | b) Uses telephone if number given verbally/visually or predialed |
| | ☐ | c) Answers telephone but does not make calls |
| | ☐ | d) Unable/unwilling to use telephone at all |
| | ☐ | e) Not applicable |

CRU #044 TRIC VCI Plate #019

☐ Screening ☐ Randomization
☐ Follow Up ☐ End

**Subject ID:** ☐☐ ☐☐☐ (Centre / Subject ID)

**Date:** ☐☐☐☐ ☐☐ ☐☐ (yyyy / mm / dd)

# INFORMANT BRISTOL ACTIVITIES OF DAILY LIVING SCALE *(page 5 of 6)*

| | | |
|---|---|---|
| 16. HOUSEWORK/GARDENING | ☐ | a) Able to do housework/gardening to previous standard |
| | ☐ | b) Able to do housework/gardening but not to previous standard |
| | ☐ | c) Limited participation with a lot of supervision |
| | ☐ | d) Unwilling/unable to participate in previous activities |
| | ☐ | e) Not applicable |
| 17. SHOPPING | ☐ | a) Shops to previous standard |
| | ☐ | b) Only able to shop for 1 or 2 items with or without a list |
| | ☐ | c) Unable to shop alone, but participates when accompanied |
| | ☐ | d) Unable to participate in shopping even when accompanied |
| | ☐ | e) Not applicable |
| 18. FINANCES | ☐ | a) Responsible for own finances at previous level |
| | ☐ | b) Unable to write cheque. Can sign name & recognises money values |
| | ☐ | c) Can sign name but unable to recognise money values |
| | ☐ | d) Unable to sign name or recognise money values |
| | ☐ | e) Not applicable |

CRU #044 TRIC VCI Plate #020

☐ Screening ☐ Randomization
☐ Follow Up ☐ End

**Subject ID:** ☐☐ ☐☐☐ *Centre* *Subject ID*

**Date:** ☐☐☐☐ ☐☐ ☐☐ *yyyy* *mm* *dd*

# INFORMANT BRISTOL ACTIVITIES OF DAILY LIVING SCALE *(page 6 of 6)*

| | | |
|---|---|---|
| 19. GAMES/HOBBIES | ☐ | a) Participates in pastimes/activities to previous standard |
| | ☐ | b) Participates but needs instruction/supervision |
| | ☐ | c) Reluctant to join in, very slow needs coaxing |
| | ☐ | d) No longer able or willing to join in |
| | ☐ | e) Not applicable |

| | | |
|---|---|---|
| 20. TRANSPORT | ☐ | a) Able to drive, cycle or use public transport independently |
| | ☐ | b) Unable to drive but uses public transport or bike etc. |
| | ☐ | c) Unable to use public transport alone |
| | ☐ | d) Unable/unwilling to use transport even when accompanied |
| | ☐ | e) Not applicable |

CRU #044 TRIC VCI Plate #021 Screening

**Subject ID:** ☐☐ ☐☐☐ *Centre* *Subject ID*

**Date:** ☐☐☐☐ ☐☐ ☐☐ *yyyy* *mm* *dd*

# INFORMANT AD8 QUESTIONNAIRE

The questionnaire should be answered by a spouse, family member, friend, or caregiver. The questionnaire should be given to the respondent on a clipboard for self–administration.

| Remember, "Yes, a change" indicates that there has been a change in the last several years caused by cognitive (thinking and memory) problems. | YES, A change | NO, No change | N/A, Don't know |
|---|---|---|---|
| 1. Problems with judgment (e.g., problems making decisions, bad financial decisions, problems with thinking) | ☐ | ☐ | ☐ |
| 2. Less interest in hobbies/activities | ☐ | ☐ | ☐ |
| 3. Repeats the same things over and over (questions, stories, or statements) | ☐ | ☐ | ☐ |
| 4. Trouble learning how to use a tool, appliance, or gadget (e.g., VCR, computer, microwave, remote control) | ☐ | ☐ | ☐ |
| 5. Forgets correct month or year | ☐ | ☐ | ☐ |
| 6. Trouble handling complicated financial affairs (e.g., balancing checkbook, income taxes, paying bills) | ☐ | ☐ | ☐ |
| 7. Trouble remembering appointments | ☐ | ☐ | ☐ |
| 8. Daily problems with thinking and/or memory | ☐ | ☐ | ☐ |
| | | Total Score [0-8] | ☐ |

CRU #044 TRIC VCI Plate #022 Screening

**Subject ID:** [ ][ ] [ ][ ][ ] **Date:** [ ][ ][ ][ ] [ ][ ] [ ][ ]

Centre Subject ID yyyy mm dd

# INFORMANT IQCODE *(page 1 of 2)*

Now we want you to remember what your friend or relative was like **10 years ago** and to compare it with what he/she is like **now**. Below are situations where this person has to use his/her memory or intelligence and we want you to indicate whether this has improved, stayed the same or got worse in that situation over the past 10 years. Please place an 'X' in the appropriate box.

Note the importance of comparing his/her present performance with 10 years ago. So if 10 years ago this person always forgot where he/she had left things, and he/she still does, then this would be considered "Hasn't changed much". Please indicate the changes you have observed by circling the appropriate answer.

| | Much improved | A bit improved | Not much change | A bit worse | Much worse |
|---|---|---|---|---|---|
| 1. Remembering things about family and friends e.g. occupations, birthdays, addresses | ☐ | ☐ | ☐ | ☐ | ☐ |
| 2. Remembering things that have happened recently | ☐ | ☐ | ☐ | ☐ | ☐ |
| 3. Recalling conversations a few days later | ☐ | ☐ | ☐ | ☐ | ☐ |
| 4. Remembering his/her address and telephone number | ☐ | ☐ | ☐ | ☐ | ☐ |
| 5. Remembering what day and month it is | ☐ | ☐ | ☐ | ☐ | ☐ |
| 6. Remembering where things are usually kept | ☐ | ☐ | ☐ | ☐ | ☐ |
| 7. Remembering where to find things which have been put in a different place from usual | ☐ | ☐ | ☐ | ☐ | ☐ |
| 8. Knowing how to work familiar machines around the house | ☐ | ☐ | ☐ | ☐ | ☐ |
| 9. Learning to use a new gadget or machine around the house | ☐ | ☐ | ☐ | ☐ | ☐ |
| 10. Learning new things in general | ☐ | ☐ | ☐ | ☐ | ☐ |
| 11. Following a story in a book or on TV | ☐ | ☐ | ☐ | ☐ | ☐ |
| 12. Making decisions on everyday matters | ☐ | ☐ | ☐ | ☐ | ☐ |

CRU #044 TRIC VCI Plate #023 Screening

**Subject ID:** Centre Subject ID **Date:** yyyy mm dd

## INFORMANT IQCODE *(page 2 of 2)*

| | Much improved | A bit improved | Not much change | A bit worse | Much worse |
|---|---|---|---|---|---|
| 13. Handling money for shopping | ☐ | ☐ | ☐ | ☐ | ☐ |
| 14. Handling financial matters e.g. the pension, dealing with the bank | ☐ | ☐ | ☐ | ☐ | ☐ |
| 15. Handling other everyday arithmetic problems e.g. knowing how much food to buy, knowing how long between visits from family or friends | ☐ | ☐ | ☐ | ☐ | ☐ |
| 16. Using his/her intelligence to understand what's going on and to reason things through | ☐ | ☐ | ☐ | ☐ | ☐ |

CRU #044 TRIC VCI Plate #024

☐ Randomization ☐ End
☐ Follow Up

**Subject ID:** ☐☐ ☐☐☐ *Centre* *Subject ID*

**Date:** ☐☐☐☐ ☐☐ ☐☐ *yyyy* *mm* *dd*

# INFORMANT MBI TRACKING TOOL *(page 1 of 3)*

Please score each item for its presence over the **last 2 weeks** (continuously or on and off). If present, items should reflect a **change** from the longstanding pattern of behavior. Otherwise, check "No".

Please rate severity: **1 = Mild** (noticeable, but of minor significance); **2 = Moderate** (significant, but not dramatic); **3 = Severe** (very marked or prominent, or dramatic change). If more than 1 item in a question, rate the most severe.

| | YES | NO | SEVERITY |
|---|---|---|---|
| ***This domain describes interest, motivation, and drive*** | | | |
| Uninterested in friends, family, or home activities. | ☐ | ☐ | ☐1 ☐2 ☐3 |
| Lacking curiosity in topics that would usually have attracted interest. | ☐ | ☐ | ☐1 ☐2 ☐3 |
| Being less spontaneous and active – for example, less likely to initiate or maintain conversation. | ☐ | ☐ | ☐1 ☐2 ☐3 |
| Unmotivated to act on obligations or interests. | ☐ | ☐ | ☐1 ☐2 ☐3 |
| Lacking in affection or emotions when compared to usual self. | ☐ | ☐ | ☐1 ☐2 ☐3 |
| No longer caring about anything. | ☐ | ☐ | ☐1 ☐2 ☐3 |
| ***This domain describes mood or anxiety symptoms*** | | | |
| Sadness or being in low spirits. Episodes of tearfulness. | ☐ | ☐ | ☐1 ☐2 ☐3 |
| Less able to experience pleasure. | ☐ | ☐ | ☐1 ☐2 ☐3 |
| Feeling discouraged about the future or feeling like a failure. | ☐ | ☐ | ☐1 ☐2 ☐3 |
| Viewing self as a burden to family and friends. | ☐ | ☐ | ☐1 ☐2 ☐3 |
| Being more anxious or worried about things that are routine (e.g. events, visits, etc.). | ☐ | ☐ | ☐1 ☐2 ☐3 |
| Feeling very tense, having an inability to relax, or having shakiness, or symptoms of panic. | ☐ | ☐ | ☐1 ☐2 ☐3 |

CRU #044 TRIC VCI Plate #025

☐ Randomization ☐ End
☐ Follow Up

**Subject ID:** ☐☐ ☐☐☐ (Centre / Subject ID) **Date:** ☐☐☐☐ ☐☐ ☐☐ (yyyy / mm / dd)

## INFORMANT MBI TRACKING TOOL *(page 2 of 3)*

| | YES | NO | SEVERITY |
|---|---|---|---|
| ***This domain describes the ability to delay gratification and control behavior, impulses, oral intake and/or changes in reward*** | | | |
| Agitation, aggression, irritability, or being temperamental. | ☐ | ☐ | ☐1 ☐2 ☐3 |
| Being unreasonably or uncharacteristically argumentative. | ☐ | ☐ | ☐1 ☐2 ☐3 |
| Impulsivity. Seeming to act without considering things. | ☐ | ☐ | ☐1 ☐2 ☐3 |
| Sexually disinhibited or intrusive behaviour, such as touching (self/others), hugging, groping, etc., in a manner that is out of character or may cause offence. | ☐ | ☐ | ☐1 ☐2 ☐3 |
| Frustration or impatience. Having troubles coping with delays, or waiting for events or for one's turn? | ☐ | ☐ | ☐1 ☐2 ☐3 |
| Recklessness or lack of judgement when driving (e.g. speeding, erratic swerving, abrupt lane changes, etc.). | ☐ | ☐ | ☐1 ☐2 ☐3 |
| Stubbornness or rigidity, i.e., uncharacteristically insistent on having one's own way, or being unwilling/unable to see/hear other views. | ☐ | ☐ | ☐1 ☐2 ☐3 |
| Change in eating behaviors (e.g., overeating, cramming the mouth, insistent on eating only specific foods, or eating the food in exactly the same order). | ☐ | ☐ | ☐1 ☐2 ☐3 |
| Not finding food tasteful or enjoyable. Eating less. | ☐ | ☐ | ☐1 ☐2 ☐3 |
| Hoarding objects. | ☐ | ☐ | ☐1 ☐2 ☐3 |
| Simple repetitive behaviors or compulsions. | ☐ | ☐ | ☐1 ☐2 ☐3 |
| Trouble regulating smoking, alcohol, drug intake, gambling, or shoplifting. | ☐ | ☐ | ☐1 ☐2 ☐3 |
| ***This domain describes following societal norms and having social graces, tact, and empathy*** | | | |
| Unconcerned about how one's words or actions affect others. Insensitivity to others' feelings. | ☐ | ☐ | ☐1 ☐2 ☐3 |
| Talking openly about very personal or private matters not usually discussed in public. | ☐ | ☐ | ☐1 ☐2 ☐3 |
| Saying rude or crude things or making lewd sexual remarks. | ☐ | ☐ | ☐1 ☐2 ☐3 |
| Lacking the social judgement about what to say or how to behave in public or private. | ☐ | ☐ | ☐1 ☐2 ☐3 |
| Talking to strangers as if familiar, or intruding on their activities. | ☐ | ☐ | ☐1 ☐2 ☐3 |

CRU #044 TRIC VCI Plate #026

☐ Randomization ☐ End
☐ Follow Up

**Subject ID:** ☐☐ ☐☐☐ (Centre / Subject ID)

**Date:** ☐☐☐☐ ☐☐ ☐☐ (yyyy / mm / dd)

## INFORMANT MBI TRACKING TOOL *(page 3 of 3)*

| | YES | NO | SEVERITY |
|---|---|---|---|
| ***This domain describes strongly held beliefs and sensory experiences*** | | | |
| Having beliefs that one is in danger, or that others are planning harm or to steal one's belongings. | ☐ | ☐ | ☐1 ☐2 ☐3 |
| Suspiciousness about the intentions or motives of other people. | ☐ | ☐ | ☐1 ☐2 ☐3 |
| Unrealistic beliefs about one's power, wealth or skills. | ☐ | ☐ | ☐1 ☐2 ☐3 |
| Hearing voices or talking to imaginary people or "spirits". | ☐ | ☐ | ☐1 ☐2 ☐3 |
| Seeing things (e.g. people, animals or insects) that are not there, i.e., that are imaginary to others? | ☐ | ☐ | ☐1 ☐2 ☐3 |

CRU #044 TRIC VCI Plate #027 Randomization

**Subject ID:** ☐☐ ☐☐☐ *Centre* *Subject ID*

**Date:** ☐☐☐☐ ☐☐ ☐☐ *yyyy* *mm* *dd*

# RUN-IN PATIENT DIARY - ONCE DAILY - WEEK 1

Date that the week started on: ☐☐☐☐ ☐☐ ☐☐ *yyyy* *mm* *dd*

| Day No. | Day of the week (Mon/Tue/ Wed/Thu/ Fri/Sat/Sun) | I finished the whole treatment | I started but did not finish | I missed the treatment | Blood Pressure (mmHg) | Pain (check the number that best represents the maximum pain you experience during the session, if any) |
|---|---|---|---|---|---|---|
| 1 | ___ | ☐ | ☐ | ☐ | ☐☐☐ / ☐☐ | ☐ 0 ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10 |
| 2 | ___ | ☐ | ☐ | ☐ | ☐☐☐ / ☐☐ | ☐ 0 ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10 |
| 3 | ___ | ☐ | ☐ | ☐ | ☐☐☐ / ☐☐ | ☐ 0 ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10 |
| 4 | ___ | ☐ | ☐ | ☐ | ☐☐☐ / ☐☐ | ☐ 0 ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10 |
| 5 | ___ | ☐ | ☐ | ☐ | ☐☐☐ / ☐☐ | ☐ 0 ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10 |
| 6 | ___ | ☐ | ☐ | ☐ | ☐☐☐ / ☐☐ | ☐ 0 ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10 |
| 7 | ___ | ☐ | ☐ | ☐ | ☐☐☐ / ☐☐ | ☐ 0 ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10 |

CRU #044 TRIC VCI Plate #028 Randomization

**Subject ID:** ☐☐ (Centre) ☐☐☐ (Subject ID) **Date:** ☐☐☐☐ (yyyy) ☐☐ (mm) ☐☐ (dd)

# RUN-IN PATIENT DIARY - ONCE DAILY - WEEK 2

Date that the week started on: ☐☐☐☐ (yyyy) ☐☐ (mm) ☐☐ (dd)

| Day No. | Day of the week (Mon/Tue/ Wed/Thu/ Fri/Sat/Sun) | I finished the whole treatment | I started but did not finish | I missed the treatment | Blood Pressure (mmHg) | Pain (check the number that best represents the maximum pain you experience during the session, if any) |
|---|---|---|---|---|---|---|
| 1 | ___ | ☐ | ☐ | ☐ | ☐☐☐ / ☐☐ | ☐ 0 ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10 |
| 2 | ___ | ☐ | ☐ | ☐ | ☐☐☐ / ☐☐ | ☐ 0 ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10 |
| 3 | ___ | ☐ | ☐ | ☐ | ☐☐☐ / ☐☐ | ☐ 0 ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10 |
| 4 | ___ | ☐ | ☐ | ☐ | ☐☐☐ / ☐☐ | ☐ 0 ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10 |
| 5 | ___ | ☐ | ☐ | ☐ | ☐☐☐ / ☐☐ | ☐ 0 ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10 |
| 6 | ___ | ☐ | ☐ | ☐ | ☐☐☐ / ☐☐ | ☐ 0 ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10 |
| 7 | ___ | ☐ | ☐ | ☐ | ☐☐☐ / ☐☐ | ☐ 0 ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10 |

CRU #044 TRIC VCI Plate #029 Randomization

**Subject ID:** ☐☐ ☐☐☐ *Centre* *Subject ID*

**Date:** ☐☐☐☐ ☐☐ ☐☐ *yyyy* *mm* *dd*

# RUN-IN PATIENT DIARY - ONCE DAILY - WEEK 3

Date that the week started on: ☐☐☐☐ ☐☐ ☐☐ *yyyy* *mm* *dd*

| Day No. | Day of the week (Mon/Tue/ Wed/Thu/ Fri/Sat/Sun) | I finished the whole treatment | I started but did not finish | I missed the treatment | Blood Pressure (mmHg) | Pain (check the number that best represents the maximum pain you experience during the session, if any) |
|---|---|---|---|---|---|---|
| 1 | ___ | ☐ | ☐ | ☐ | ☐☐☐ / ☐☐ | ☐0 ☐1 ☐2 ☐3 ☐4 ☐5 ☐6 ☐7 ☐8 ☐9 ☐10 |
| 2 | ___ | ☐ | ☐ | ☐ | ☐☐☐ / ☐☐ | ☐0 ☐1 ☐2 ☐3 ☐4 ☐5 ☐6 ☐7 ☐8 ☐9 ☐10 |
| 3 | ___ | ☐ | ☐ | ☐ | ☐☐☐ / ☐☐ | ☐0 ☐1 ☐2 ☐3 ☐4 ☐5 ☐6 ☐7 ☐8 ☐9 ☐10 |
| 4 | ___ | ☐ | ☐ | ☐ | ☐☐☐ / ☐☐ | ☐0 ☐1 ☐2 ☐3 ☐4 ☐5 ☐6 ☐7 ☐8 ☐9 ☐10 |
| 5 | ___ | ☐ | ☐ | ☐ | ☐☐☐ / ☐☐ | ☐0 ☐1 ☐2 ☐3 ☐4 ☐5 ☐6 ☐7 ☐8 ☐9 ☐10 |
| 6 | ___ | ☐ | ☐ | ☐ | ☐☐☐ / ☐☐ | ☐0 ☐1 ☐2 ☐3 ☐4 ☐5 ☐6 ☐7 ☐8 ☐9 ☐10 |
| 7 | ___ | ☐ | ☐ | ☐ | ☐☐☐ / ☐☐ | ☐0 ☐1 ☐2 ☐3 ☐4 ☐5 ☐6 ☐7 ☐8 ☐9 ☐10 |

CRU #044 TRIC VCI Plate #030 Follow Up

**Subject ID:** ☐☐ ☐☐☐ *Centre* *Subject ID*

**Date:** ☐☐☐☐ ☐☐ ☐☐ *yyyy* *mm* *dd*

# PATIENT DIARY - ONCE DAILY - WEEK 1

Date that the week started on: ☐☐☐☐ ☐☐ ☐☐ *yyyy* *mm* *dd*

| Day No. | Day of the week (Mon/Tue/ Wed/Thu/ Fri/Sat/Sun) | I finished the whole treatment | I started but did not finish | I missed the treatment | Blood Pressure (mmHg) | Pain (check the number that best represents the maximum pain you experience during the session, if any) |
|---|---|---|---|---|---|---|
| 1 | ___ | ☐ | ☐ | ☐ | ☐☐☐ / ☐☐ | ☐0 ☐1 ☐2 ☐3 ☐4 ☐5 ☐6 ☐7 ☐8 ☐9 ☐10 |
| 2 | ___ | ☐ | ☐ | ☐ | ☐☐☐ / ☐☐ | ☐0 ☐1 ☐2 ☐3 ☐4 ☐5 ☐6 ☐7 ☐8 ☐9 ☐10 |
| 3 | ___ | ☐ | ☐ | ☐ | ☐☐☐ / ☐☐ | ☐0 ☐1 ☐2 ☐3 ☐4 ☐5 ☐6 ☐7 ☐8 ☐9 ☐10 |
| 4 | ___ | ☐ | ☐ | ☐ | ☐☐☐ / ☐☐ | ☐0 ☐1 ☐2 ☐3 ☐4 ☐5 ☐6 ☐7 ☐8 ☐9 ☐10 |
| 5 | ___ | ☐ | ☐ | ☐ | ☐☐☐ / ☐☐ | ☐0 ☐1 ☐2 ☐3 ☐4 ☐5 ☐6 ☐7 ☐8 ☐9 ☐10 |
| 6 | ___ | ☐ | ☐ | ☐ | ☐☐☐ / ☐☐ | ☐0 ☐1 ☐2 ☐3 ☐4 ☐5 ☐6 ☐7 ☐8 ☐9 ☐10 |
| 7 | ___ | ☐ | ☐ | ☐ | ☐☐☐ / ☐☐ | ☐0 ☐1 ☐2 ☐3 ☐4 ☐5 ☐6 ☐7 ☐8 ☐9 ☐10 |

CRU #044 TRIC VCI Plate #031 Follow Up

**Subject ID:** ☐☐ ☐☐☐ *Centre* *Subject ID*

**Date:** ☐☐☐☐ ☐☐ ☐☐ *yyyy* *mm* *dd*

# PATIENT DIARY - ONCE DAILY - WEEK 2

Date that the week started on: ☐☐☐☐ ☐☐ ☐☐ *yyyy* *mm* *dd*

| Day No. | Day of the week (Mon/Tue/ Wed/Thu/ Fri/Sat/Sun) | I finished the whole treatment | I started but did not finish | I missed the treatment | Blood Pressure (mmHg) | Pain (check the number that best represents the maximum pain you experience during the session, if any) |
|---|---|---|---|---|---|---|
| 1 | ___ | ☐ | ☐ | ☐ | ☐☐☐ / ☐☐ | ☐0 ☐1 ☐2 ☐3 ☐4 ☐5 ☐6 ☐7 ☐8 ☐9 ☐10 |
| 2 | ___ | ☐ | ☐ | ☐ | ☐☐☐ / ☐☐ | ☐0 ☐1 ☐2 ☐3 ☐4 ☐5 ☐6 ☐7 ☐8 ☐9 ☐10 |
| 3 | ___ | ☐ | ☐ | ☐ | ☐☐☐ / ☐☐ | ☐0 ☐1 ☐2 ☐3 ☐4 ☐5 ☐6 ☐7 ☐8 ☐9 ☐10 |
| 4 | ___ | ☐ | ☐ | ☐ | ☐☐☐ / ☐☐ | ☐0 ☐1 ☐2 ☐3 ☐4 ☐5 ☐6 ☐7 ☐8 ☐9 ☐10 |
| 5 | ___ | ☐ | ☐ | ☐ | ☐☐☐ / ☐☐ | ☐0 ☐1 ☐2 ☐3 ☐4 ☐5 ☐6 ☐7 ☐8 ☐9 ☐10 |
| 6 | ___ | ☐ | ☐ | ☐ | ☐☐☐ / ☐☐ | ☐0 ☐1 ☐2 ☐3 ☐4 ☐5 ☐6 ☐7 ☐8 ☐9 ☐10 |
| 7 | ___ | ☐ | ☐ | ☐ | ☐☐☐ / ☐☐ | ☐0 ☐1 ☐2 ☐3 ☐4 ☐5 ☐6 ☐7 ☐8 ☐9 ☐10 |

CRU #044 TRIC VCI Plate #032 Follow Up

**Subject ID:** ☐☐ ☐☐☐ *Centre* *Subject ID*

**Date:** ☐☐☐☐ ☐☐ ☐☐ *yyyy* *mm* *dd*

# PATIENT DIARY - ONCE DAILY - WEEK 3

Date that the week started on: ☐☐☐☐ ☐☐ ☐☐ *yyyy* *mm* *dd*

| Day No. | Day of the week (Mon/Tue/ Wed/Thu/ Fri/Sat/Sun) | I finished the whole treatment | I started but did not finish | I missed the treatment | Blood Pressure (mmHg) | Pain (check the number that best represents the maximum pain you experience during the session, if any) |
|---|---|---|---|---|---|---|
| 1 | ___ | ☐ | ☐ | ☐ | ☐☐☐ / ☐☐ | ☐0 ☐1 ☐2 ☐3 ☐4 ☐5 ☐6 ☐7 ☐8 ☐9 ☐10 |
| 2 | ___ | ☐ | ☐ | ☐ | ☐☐☐ / ☐☐ | ☐0 ☐1 ☐2 ☐3 ☐4 ☐5 ☐6 ☐7 ☐8 ☐9 ☐10 |
| 3 | ___ | ☐ | ☐ | ☐ | ☐☐☐ / ☐☐ | ☐0 ☐1 ☐2 ☐3 ☐4 ☐5 ☐6 ☐7 ☐8 ☐9 ☐10 |
| 4 | ___ | ☐ | ☐ | ☐ | ☐☐☐ / ☐☐ | ☐0 ☐1 ☐2 ☐3 ☐4 ☐5 ☐6 ☐7 ☐8 ☐9 ☐10 |
| 5 | ___ | ☐ | ☐ | ☐ | ☐☐☐ / ☐☐ | ☐0 ☐1 ☐2 ☐3 ☐4 ☐5 ☐6 ☐7 ☐8 ☐9 ☐10 |
| 6 | ___ | ☐ | ☐ | ☐ | ☐☐☐ / ☐☐ | ☐0 ☐1 ☐2 ☐3 ☐4 ☐5 ☐6 ☐7 ☐8 ☐9 ☐10 |
| 7 | ___ | ☐ | ☐ | ☐ | ☐☐☐ / ☐☐ | ☐0 ☐1 ☐2 ☐3 ☐4 ☐5 ☐6 ☐7 ☐8 ☐9 ☐10 |

CRU #044 TRIC VCI Plate #033 Follow Up

**Subject ID:** ☐☐ ☐☐☐ *Centre* *Subject ID*

**Date:** ☐☐☐☐ ☐☐ ☐☐ *yyyy* *mm* *dd*

# PATIENT DIARY - ONCE DAILY - WEEK 4

Date that the week started on: ☐☐☐☐ ☐☐ ☐☐ *yyyy* *mm* *dd*

| Day No. | Day of the week (Mon/Tue/ Wed/Thu/ Fri/Sat/Sun) | I finished the whole treatment | I started but did not finish | I missed the treatment | Blood Pressure (mmHg) | Pain (check the number that best represents the maximum pain you experience during the session, if any) |
|---|---|---|---|---|---|---|
| 1 | ___ | ☐ | ☐ | ☐ | ☐☐☐ / ☐☐ | ☐0 ☐1 ☐2 ☐3 ☐4 ☐5 ☐6 ☐7 ☐8 ☐9 ☐10 |
| 2 | ___ | ☐ | ☐ | ☐ | ☐☐☐ / ☐☐ | ☐0 ☐1 ☐2 ☐3 ☐4 ☐5 ☐6 ☐7 ☐8 ☐9 ☐10 |
| 3 | ___ | ☐ | ☐ | ☐ | ☐☐☐ / ☐☐ | ☐0 ☐1 ☐2 ☐3 ☐4 ☐5 ☐6 ☐7 ☐8 ☐9 ☐10 |
| 4 | ___ | ☐ | ☐ | ☐ | ☐☐☐ / ☐☐ | ☐0 ☐1 ☐2 ☐3 ☐4 ☐5 ☐6 ☐7 ☐8 ☐9 ☐10 |
| 5 | ___ | ☐ | ☐ | ☐ | ☐☐☐ / ☐☐ | ☐0 ☐1 ☐2 ☐3 ☐4 ☐5 ☐6 ☐7 ☐8 ☐9 ☐10 |
| 6 | ___ | ☐ | ☐ | ☐ | ☐☐☐ / ☐☐ | ☐0 ☐1 ☐2 ☐3 ☐4 ☐5 ☐6 ☐7 ☐8 ☐9 ☐10 |
| 7 | ___ | ☐ | ☐ | ☐ | ☐☐☐ / ☐☐ | ☐0 ☐1 ☐2 ☐3 ☐4 ☐5 ☐6 ☐7 ☐8 ☐9 ☐10 |

CRU #044 TRIC VCI Plate #034 Follow Up

**Subject ID:** ☐☐ ☐☐☐ *Centre* *Subject ID*

**Date:** ☐☐☐☐ ☐☐ ☐☐ *yyyy* *mm* *dd*

# PATIENT DIARY - ONCE DAILY - WEEK 5

Date that the week started on: ☐☐☐☐ ☐☐ ☐☐ *yyyy* *mm* *dd*

| Day No. | Day of the week (Mon/Tue/ Wed/Thu/ Fri/Sat/Sun) | I finished the whole treatment | I started but did not finish | I missed the treatment | Blood Pressure (mmHg) | Pain (check the number that best represents the maximum pain you experience during the session, if any) |
|---|---|---|---|---|---|---|
| 1 | ___ | ☐ | ☐ | ☐ | ☐☐☐ / ☐☐ | ☐0 ☐1 ☐2 ☐3 ☐4 ☐5 ☐6 ☐7 ☐8 ☐9 ☐10 |
| 2 | ___ | ☐ | ☐ | ☐ | ☐☐☐ / ☐☐ | ☐0 ☐1 ☐2 ☐3 ☐4 ☐5 ☐6 ☐7 ☐8 ☐9 ☐10 |
| 3 | ___ | ☐ | ☐ | ☐ | ☐☐☐ / ☐☐ | ☐0 ☐1 ☐2 ☐3 ☐4 ☐5 ☐6 ☐7 ☐8 ☐9 ☐10 |
| 4 | ___ | ☐ | ☐ | ☐ | ☐☐☐ / ☐☐ | ☐0 ☐1 ☐2 ☐3 ☐4 ☐5 ☐6 ☐7 ☐8 ☐9 ☐10 |
| 5 | ___ | ☐ | ☐ | ☐ | ☐☐☐ / ☐☐ | ☐0 ☐1 ☐2 ☐3 ☐4 ☐5 ☐6 ☐7 ☐8 ☐9 ☐10 |
| 6 | ___ | ☐ | ☐ | ☐ | ☐☐☐ / ☐☐ | ☐0 ☐1 ☐2 ☐3 ☐4 ☐5 ☐6 ☐7 ☐8 ☐9 ☐10 |
| 7 | ___ | ☐ | ☐ | ☐ | ☐☐☐ / ☐☐ | ☐0 ☐1 ☐2 ☐3 ☐4 ☐5 ☐6 ☐7 ☐8 ☐9 ☐10 |

CRU #044 TRIC VCI Plate #035 Follow Up

**Subject ID:** ☐☐ ☐☐☐ (Centre / Subject ID)

**Date:** ☐☐☐☐ ☐☐ ☐☐ (yyyy / mm / dd)

# PATIENT DIARY - TWICE DAILY - WEEK 1 *(page 1 of 2)*

Date that the week started on: ☐☐☐☐ ☐☐ ☐☐ (yyyy / mm / dd)

| Day No. | Day of the week (Mon/Tue/Wed/Thu/Fri/Sat/Sun) | Time | I finished the whole treatment | I started but did not finish | I missed the treament | Blood Pressure (mmHg) | Pain (check the number that best represents the maximum pain you experience during the session, if any) |
|---|---|---|---|---|---|---|---|
| 1 | — — — | AM | ☐ | ☐ | ☐ | ☐☐☐ / ☐☐ | ☐0 ☐1 ☐2 ☐3 ☐4 ☐5 ☐6 ☐7 ☐8 ☐9 ☐10 |
| | | PM | ☐ | ☐ | ☐ | ☐☐☐ / ☐☐ | ☐0 ☐1 ☐2 ☐3 ☐4 ☐5 ☐6 ☐7 ☐8 ☐9 ☐10 |
| 2 | | AM | ☐ | ☐ | ☐ | ☐☐☐ / ☐☐ | ☐0 ☐1 ☐2 ☐3 ☐4 ☐5 ☐6 ☐7 ☐8 ☐9 ☐10 |
| | | PM | ☐ | ☐ | ☐ | ☐☐☐ / ☐☐ | ☐0 ☐1 ☐2 ☐3 ☐4 ☐5 ☐6 ☐7 ☐8 ☐9 ☐10 |
| 3 | | AM | ☐ | ☐ | ☐ | ☐☐☐ / ☐☐ | ☐0 ☐1 ☐2 ☐3 ☐4 ☐5 ☐6 ☐7 ☐8 ☐9 ☐10 |
| | | PM | ☐ | ☐ | ☐ | ☐☐☐ / ☐☐ | ☐0 ☐1 ☐2 ☐3 ☐4 ☐5 ☐6 ☐7 ☐8 ☐9 ☐10 |

CRU #044 TRIC VCI Plate #036 Follow Up

**Subject ID:** ☐☐ ☐☐☐ *Centre* *Subject ID*

**Date:** ☐☐☐☐ ☐☐ ☐☐ *yyyy* *mm* *dd*

# PATIENT DIARY - TWICE DAILY - WEEK 1 *(page 2 of 2)*

| Day No. | Day of the week (Mon/Tue/Wed/Thu/Fri/Sat/Sun) | Time | I finished the whole treatment | I started but did not finish | I missed the treament | Blood Pressure (mmHg) | Pain (check the number that best represents the maximum pain you experience during the session, if any) |
|---|---|---|---|---|---|---|---|
| 4 | ___ | AM | ☐ | ☐ | ☐ | ☐☐☐ / ☐☐ | ☐0 ☐1 ☐2 ☐3 ☐4 ☐5 ☐6 ☐7 ☐8 ☐9 ☐10 |
| | | PM | ☐ | ☐ | ☐ | ☐☐☐ / ☐☐ | ☐0 ☐1 ☐2 ☐3 ☐4 ☐5 ☐6 ☐7 ☐8 ☐9 ☐10 |
| 5 | ___ | AM | ☐ | ☐ | ☐ | ☐☐☐ / ☐☐ | ☐0 ☐1 ☐2 ☐3 ☐4 ☐5 ☐6 ☐7 ☐8 ☐9 ☐10 |
| | | PM | ☐ | ☐ | ☐ | ☐☐☐ / ☐☐ | ☐0 ☐1 ☐2 ☐3 ☐4 ☐5 ☐6 ☐7 ☐8 ☐9 ☐10 |
| 6 | ___ | AM | ☐ | ☐ | ☐ | ☐☐☐ / ☐☐ | ☐0 ☐1 ☐2 ☐3 ☐4 ☐5 ☐6 ☐7 ☐8 ☐9 ☐10 |
| | | PM | ☐ | ☐ | ☐ | ☐☐☐ / ☐☐ | ☐0 ☐1 ☐2 ☐3 ☐4 ☐5 ☐6 ☐7 ☐8 ☐9 ☐10 |
| 7 | ___ | AM | ☐ | ☐ | ☐ | ☐☐☐ / ☐☐ | ☐0 ☐1 ☐2 ☐3 ☐4 ☐5 ☐6 ☐7 ☐8 ☐9 ☐10 |
| | | PM | ☐ | ☐ | ☐ | ☐☐☐ / ☐☐ | ☐0 ☐1 ☐2 ☐3 ☐4 ☐5 ☐6 ☐7 ☐8 ☐9 ☐10 |

CRU #044 TRIC VCI Plate #037 Follow Up

**Subject ID:** ☐☐ ☐☐☐ *Centre* *Subject ID*

**Date:** ☐☐☐☐ ☐☐ ☐☐ *yyyy* *mm* *dd*

# PATIENT DIARY - TWICE DAILY - WEEK 2 *(page 1 of 2)*

Date that the week started on: ☐☐☐☐ ☐☐ ☐☐ *yyyy* *mm* *dd*

| Day No. | Day of the week (Mon/Tue/Wed/Thu/Fri/Sat/Sun) | Time | I finished the whole treatment | I started but did not finish | I missed the treament | Blood Pressure (mmHg) | Pain (check the number that best represents the maximum pain you experience during the session, if any) |
|---|---|---|---|---|---|---|---|
| 1 | — — — | AM | ☐ | ☐ | ☐ | ☐☐☐ / ☐☐ | ☐0 ☐1 ☐2 ☐3 ☐4 ☐5 ☐6 ☐7 ☐8 ☐9 ☐10 |
| | | PM | ☐ | ☐ | ☐ | ☐☐☐ / ☐☐ | ☐0 ☐1 ☐2 ☐3 ☐4 ☐5 ☐6 ☐7 ☐8 ☐9 ☐10 |
| 2 | | AM | ☐ | ☐ | ☐ | ☐☐☐ / ☐☐ | ☐0 ☐1 ☐2 ☐3 ☐4 ☐5 ☐6 ☐7 ☐8 ☐9 ☐10 |
| | | PM | ☐ | ☐ | ☐ | ☐☐☐ / ☐☐ | ☐0 ☐1 ☐2 ☐3 ☐4 ☐5 ☐6 ☐7 ☐8 ☐9 ☐10 |
| 3 | | AM | ☐ | ☐ | ☐ | ☐☐☐ / ☐☐ | ☐0 ☐1 ☐2 ☐3 ☐4 ☐5 ☐6 ☐7 ☐8 ☐9 ☐10 |
| | | PM | ☐ | ☐ | ☐ | ☐☐☐ / ☐☐ | ☐0 ☐1 ☐2 ☐3 ☐4 ☐5 ☐6 ☐7 ☐8 ☐9 ☐10 |

CRU #044 TRIC VCI Plate #038 Follow Up

**Subject ID:** ☐☐ ☐☐☐ (Centre / Subject ID) **Date:** ☐☐☐☐ ☐☐ ☐☐ (yyyy / mm / dd)

# PATIENT DIARY - TWICE DAILY - WEEK 2 *(page 2 of 2)*

| Day No. | Day of the week (Mon/Tue/Wed/Thu/Fri/Sat/Sun) | Time | I finished the whole treatment | I started but did not finish | I missed the treament | Blood Pressure (mmHg) | Pain (check the number that best represents the maximum pain you experience during the session, if any) |
|---|---|---|---|---|---|---|---|
| 4 | ___ | AM | ☐ | ☐ | ☐ | ☐☐☐/☐☐ | ☐0 ☐1 ☐2 ☐3 ☐4 ☐5 ☐6 ☐7 ☐8 ☐9 ☐10 |
| | | PM | ☐ | ☐ | ☐ | ☐☐☐/☐☐ | ☐0 ☐1 ☐2 ☐3 ☐4 ☐5 ☐6 ☐7 ☐8 ☐9 ☐10 |
| 5 | ___ | AM | ☐ | ☐ | ☐ | ☐☐☐/☐☐ | ☐0 ☐1 ☐2 ☐3 ☐4 ☐5 ☐6 ☐7 ☐8 ☐9 ☐10 |
| | | PM | ☐ | ☐ | ☐ | ☐☐☐/☐☐ | ☐0 ☐1 ☐2 ☐3 ☐4 ☐5 ☐6 ☐7 ☐8 ☐9 ☐10 |
| 6 | ___ | AM | ☐ | ☐ | ☐ | ☐☐☐/☐☐ | ☐0 ☐1 ☐2 ☐3 ☐4 ☐5 ☐6 ☐7 ☐8 ☐9 ☐10 |
| | | PM | ☐ | ☐ | ☐ | ☐☐☐/☐☐ | ☐0 ☐1 ☐2 ☐3 ☐4 ☐5 ☐6 ☐7 ☐8 ☐9 ☐10 |
| 7 | ___ | AM | ☐ | ☐ | ☐ | ☐☐☐/☐☐ | ☐0 ☐1 ☐2 ☐3 ☐4 ☐5 ☐6 ☐7 ☐8 ☐9 ☐10 |
| | | PM | ☐ | ☐ | ☐ | ☐☐☐/☐☐ | ☐0 ☐1 ☐2 ☐3 ☐4 ☐5 ☐6 ☐7 ☐8 ☐9 ☐10 |

CRU #044 TRIC VCI Plate #039 Follow Up

**Subject ID:** ☐☐ ☐☐☐ (Centre / Subject ID) **Date:** ☐☐☐☐ ☐☐ ☐☐ (yyyy / mm / dd)

# PATIENT DIARY - TWICE DAILY - WEEK 3 *(page 1 of 2)*

Date that the week started on: ☐☐☐☐ ☐☐ ☐☐ (yyyy / mm / dd)

| Day No. | Day of the week (Mon/Tue/Wed/Thu/Fri/Sat/Sun) | Time | I finished the whole treatment | I started but did not finish | I missed the treament | Blood Pressure (mmHg) | Pain (check the number that best represents the maximum pain you experience during the session, if any) |
|---|---|---|---|---|---|---|---|
| 1 | — — — | AM | ☐ | ☐ | ☐ | ☐☐☐ / ☐☐ | ☐0 ☐1 ☐2 ☐3 ☐4 ☐5 ☐6 ☐7 ☐8 ☐9 ☐10 |
| | | PM | ☐ | ☐ | ☐ | ☐☐☐ / ☐☐ | ☐0 ☐1 ☐2 ☐3 ☐4 ☐5 ☐6 ☐7 ☐8 ☐9 ☐10 |
| 2 | | AM | ☐ | ☐ | ☐ | ☐☐☐ / ☐☐ | ☐0 ☐1 ☐2 ☐3 ☐4 ☐5 ☐6 ☐7 ☐8 ☐9 ☐10 |
| | | PM | ☐ | ☐ | ☐ | ☐☐☐ / ☐☐ | ☐0 ☐1 ☐2 ☐3 ☐4 ☐5 ☐6 ☐7 ☐8 ☐9 ☐10 |
| 3 | | AM | ☐ | ☐ | ☐ | ☐☐☐ / ☐☐ | ☐0 ☐1 ☐2 ☐3 ☐4 ☐5 ☐6 ☐7 ☐8 ☐9 ☐10 |
| | | PM | ☐ | ☐ | ☐ | ☐☐☐ / ☐☐ | ☐0 ☐1 ☐2 ☐3 ☐4 ☐5 ☐6 ☐7 ☐8 ☐9 ☐10 |

CRU #044 TRIC VCI Plate #040 Follow Up

**Subject ID:** ☐☐ ☐☐☐ *Centre* *Subject ID*

**Date:** ☐☐☐☐ ☐☐ ☐☐ *yyyy* *mm* *dd*

# PATIENT DIARY - TWICE DAILY - WEEK 3 *(page 2 of 2)*

| Day No. | Day of the week (Mon/Tue/Wed/Thu/Fri/Sat/Sun) | Time | I finished the whole treatment | I started but did not finish | I missed the treament | Blood Pressure (mmHg) | Pain (check the number that best represents the maximum pain you experience during the session, if any) |
|---|---|---|---|---|---|---|---|
| 4 | ___ | AM | ☐ | ☐ | ☐ | ☐☐☐ / ☐☐ | ☐0 ☐1 ☐2 ☐3 ☐4 ☐5 ☐6 ☐7 ☐8 ☐9 ☐10 |
| | | PM | ☐ | ☐ | ☐ | ☐☐☐ / ☐☐ | ☐0 ☐1 ☐2 ☐3 ☐4 ☐5 ☐6 ☐7 ☐8 ☐9 ☐10 |
| 5 | ___ | AM | ☐ | ☐ | ☐ | ☐☐☐ / ☐☐ | ☐0 ☐1 ☐2 ☐3 ☐4 ☐5 ☐6 ☐7 ☐8 ☐9 ☐10 |
| | | PM | ☐ | ☐ | ☐ | ☐☐☐ / ☐☐ | ☐0 ☐1 ☐2 ☐3 ☐4 ☐5 ☐6 ☐7 ☐8 ☐9 ☐10 |
| 6 | ___ | AM | ☐ | ☐ | ☐ | ☐☐☐ / ☐☐ | ☐0 ☐1 ☐2 ☐3 ☐4 ☐5 ☐6 ☐7 ☐8 ☐9 ☐10 |
| | | PM | ☐ | ☐ | ☐ | ☐☐☐ / ☐☐ | ☐0 ☐1 ☐2 ☐3 ☐4 ☐5 ☐6 ☐7 ☐8 ☐9 ☐10 |
| 7 | ___ | AM | ☐ | ☐ | ☐ | ☐☐☐ / ☐☐ | ☐0 ☐1 ☐2 ☐3 ☐4 ☐5 ☐6 ☐7 ☐8 ☐9 ☐10 |
| | | PM | ☐ | ☐ | ☐ | ☐☐☐ / ☐☐ | ☐0 ☐1 ☐2 ☐3 ☐4 ☐5 ☐6 ☐7 ☐8 ☐9 ☐10 |

CRU #044 TRIC VCI Plate #041 Follow Up

**Subject ID:** ☐☐ ☐☐☐ (Centre / Subject ID)

**Date:** ☐☐☐☐ ☐☐ ☐☐ (yyyy / mm / dd)

# PATIENT DIARY - TWICE DAILY - WEEK 4 *(page 1 of 2)*

Date that the week started on: ☐☐☐☐ ☐☐ ☐☐ (yyyy / mm / dd)

| Day No. | Day of the week (Mon/Tue/Wed/Thu/Fri/Sat/Sun) | Time | I finished the whole treatment | I started but did not finish | I missed the treament | Blood Pressure (mmHg) | Pain (check the number that best represents the maximum pain you experience during the session, if any) |
|---|---|---|---|---|---|---|---|
| 1 | — — — | AM | ☐ | ☐ | ☐ | ☐☐☐ / ☐☐ | ☐0 ☐1 ☐2 ☐3 ☐4 ☐5 ☐6 ☐7 ☐8 ☐9 ☐10 |
| | | PM | ☐ | ☐ | ☐ | ☐☐☐ / ☐☐ | ☐0 ☐1 ☐2 ☐3 ☐4 ☐5 ☐6 ☐7 ☐8 ☐9 ☐10 |
| 2 | | AM | ☐ | ☐ | ☐ | ☐☐☐ / ☐☐ | ☐0 ☐1 ☐2 ☐3 ☐4 ☐5 ☐6 ☐7 ☐8 ☐9 ☐10 |
| | | PM | ☐ | ☐ | ☐ | ☐☐☐ / ☐☐ | ☐0 ☐1 ☐2 ☐3 ☐4 ☐5 ☐6 ☐7 ☐8 ☐9 ☐10 |
| 3 | | AM | ☐ | ☐ | ☐ | ☐☐☐ / ☐☐ | ☐0 ☐1 ☐2 ☐3 ☐4 ☐5 ☐6 ☐7 ☐8 ☐9 ☐10 |
| | | PM | ☐ | ☐ | ☐ | ☐☐☐ / ☐☐ | ☐0 ☐1 ☐2 ☐3 ☐4 ☐5 ☐6 ☐7 ☐8 ☐9 ☐10 |

CRU #044 TRIC VCI Plate #042 Follow Up

**Subject ID:** ☐☐ ☐☐☐ *Centre* *Subject ID*

**Date:** ☐☐☐☐ ☐☐ ☐☐ *yyyy* *mm* *dd*

# PATIENT DIARY - TWICE DAILY - WEEK 4 *(page 2 of 2)*

| Day No. | Day of the week (Mon/Tue/Wed/Thu/Fri/Sat/Sun) | Time | I finished the whole treatment | I started but did not finish | I missed the treament | Blood Pressure (mmHg) | Pain (check the number that best represents the maximum pain you experience during the session, if any) |
|---|---|---|---|---|---|---|---|
| 4 | ___ | AM | ☐ | ☐ | ☐ | ☐☐☐ / ☐☐ | ☐0 ☐1 ☐2 ☐3 ☐4 ☐5 ☐6 ☐7 ☐8 ☐9 ☐10 |
| | | PM | ☐ | ☐ | ☐ | ☐☐☐ / ☐☐ | ☐0 ☐1 ☐2 ☐3 ☐4 ☐5 ☐6 ☐7 ☐8 ☐9 ☐10 |
| 5 | ___ | AM | ☐ | ☐ | ☐ | ☐☐☐ / ☐☐ | ☐0 ☐1 ☐2 ☐3 ☐4 ☐5 ☐6 ☐7 ☐8 ☐9 ☐10 |
| | | PM | ☐ | ☐ | ☐ | ☐☐☐ / ☐☐ | ☐0 ☐1 ☐2 ☐3 ☐4 ☐5 ☐6 ☐7 ☐8 ☐9 ☐10 |
| 6 | ___ | AM | ☐ | ☐ | ☐ | ☐☐☐ / ☐☐ | ☐0 ☐1 ☐2 ☐3 ☐4 ☐5 ☐6 ☐7 ☐8 ☐9 ☐10 |
| | | PM | ☐ | ☐ | ☐ | ☐☐☐ / ☐☐ | ☐0 ☐1 ☐2 ☐3 ☐4 ☐5 ☐6 ☐7 ☐8 ☐9 ☐10 |
| 7 | ___ | AM | ☐ | ☐ | ☐ | ☐☐☐ / ☐☐ | ☐0 ☐1 ☐2 ☐3 ☐4 ☐5 ☐6 ☐7 ☐8 ☐9 ☐10 |
| | | PM | ☐ | ☐ | ☐ | ☐☐☐ / ☐☐ | ☐0 ☐1 ☐2 ☐3 ☐4 ☐5 ☐6 ☐7 ☐8 ☐9 ☐10 |

CRU #044 TRIC VCI  Plate #043  Follow Up

**Subject ID:** ☐☐ ☐☐☐ (Centre / Subject ID)  **Date:** ☐☐☐☐ ☐☐ ☐☐ (yyyy / mm / dd)

# PATIENT DIARY - TWICE DAILY - WEEK 5 *(page 1 of 2)*

Date that the week started on: ☐☐☐☐ ☐☐ ☐☐ (yyyy / mm / dd)

| Day No. | Day of the week (Mon/Tue/Wed/Thu/Fri/Sat/Sun) | Time | I finished the whole treatment | I started but did not finish | I missed the treament | Blood Pressure (mmHg) | Pain (check the number that best represents the maximum pain you experience during the session, if any) |
|---|---|---|---|---|---|---|---|
| 1 | — — — | AM | ☐ | ☐ | ☐ | ☐☐☐ / ☐☐ | ☐0 ☐1 ☐2 ☐3 ☐4 ☐5 ☐6 ☐7 ☐8 ☐9 ☐10 |
| | | PM | ☐ | ☐ | ☐ | ☐☐☐ / ☐☐ | ☐0 ☐1 ☐2 ☐3 ☐4 ☐5 ☐6 ☐7 ☐8 ☐9 ☐10 |
| 2 | | AM | ☐ | ☐ | ☐ | ☐☐☐ / ☐☐ | ☐0 ☐1 ☐2 ☐3 ☐4 ☐5 ☐6 ☐7 ☐8 ☐9 ☐10 |
| | | PM | ☐ | ☐ | ☐ | ☐☐☐ / ☐☐ | ☐0 ☐1 ☐2 ☐3 ☐4 ☐5 ☐6 ☐7 ☐8 ☐9 ☐10 |
| 3 | | AM | ☐ | ☐ | ☐ | ☐☐☐ / ☐☐ | ☐0 ☐1 ☐2 ☐3 ☐4 ☐5 ☐6 ☐7 ☐8 ☐9 ☐10 |
| | | PM | ☐ | ☐ | ☐ | ☐☐☐ / ☐☐ | ☐0 ☐1 ☐2 ☐3 ☐4 ☐5 ☐6 ☐7 ☐8 ☐9 ☐10 |

CRU #044 TRIC VCI Plate #044 Follow Up

**Subject ID:** ☐☐ ☐☐☐ *Centre* *Subject ID*

**Date:** ☐☐☐☐ ☐☐ ☐☐ *yyyy* *mm* *dd*

# PATIENT DIARY - TWICE DAILY - WEEK 5 *(page 2 of 2)*

| Day No. | Day of the week (Mon/Tue/Wed/Thu/Fri/Sat/Sun) | Time | I finished the whole treatment | I started but did not finish | I missed the treament | Blood Pressure (mmHg) | Pain (check the number that best represents the maximum pain you experience during the session, if any) |
|---|---|---|---|---|---|---|---|
| 4 | ___ | AM | ☐ | ☐ | ☐ | ☐☐☐ / ☐☐ | ☐0 ☐1 ☐2 ☐3 ☐4 ☐5 ☐6 ☐7 ☐8 ☐9 ☐10 |
| | | PM | ☐ | ☐ | ☐ | ☐☐☐ / ☐☐ | ☐0 ☐1 ☐2 ☐3 ☐4 ☐5 ☐6 ☐7 ☐8 ☐9 ☐10 |
| 5 | ___ | AM | ☐ | ☐ | ☐ | ☐☐☐ / ☐☐ | ☐0 ☐1 ☐2 ☐3 ☐4 ☐5 ☐6 ☐7 ☐8 ☐9 ☐10 |
| | | PM | ☐ | ☐ | ☐ | ☐☐☐ / ☐☐ | ☐0 ☐1 ☐2 ☐3 ☐4 ☐5 ☐6 ☐7 ☐8 ☐9 ☐10 |
| 6 | ___ | AM | ☐ | ☐ | ☐ | ☐☐☐ / ☐☐ | ☐0 ☐1 ☐2 ☐3 ☐4 ☐5 ☐6 ☐7 ☐8 ☐9 ☐10 |
| | | PM | ☐ | ☐ | ☐ | ☐☐☐ / ☐☐ | ☐0 ☐1 ☐2 ☐3 ☐4 ☐5 ☐6 ☐7 ☐8 ☐9 ☐10 |
| 7 | ___ | AM | ☐ | ☐ | ☐ | ☐☐☐ / ☐☐ | ☐0 ☐1 ☐2 ☐3 ☐4 ☐5 ☐6 ☐7 ☐8 ☐9 ☐10 |
| | | PM | ☐ | ☐ | ☐ | ☐☐☐ / ☐☐ | ☐0 ☐1 ☐2 ☐3 ☐4 ☐5 ☐6 ☐7 ☐8 ☐9 ☐10 |

CRU #044 TRIC VCI Plate #045 Randomization

**Subject ID:** ☐☐ ☐☐☐ (Centre / Subject ID) **Date:** ☐☐☐☐ ☐☐ ☐☐ (yyyy / mm / dd)

## RANDOMIZATION

| | | |
|---|---|---|
| Was informed consent obtained? | ☐ Yes | ☐ No |
| Is the participant eligible for randomization? | ☐ Yes | ☐ No |
| Randomization assignment | ☐ Once Daily Treatment | ☐ Twice Daily Treatment |

| | |
|---|---|
| Signature: _____ | Date: ☐☐☐☐ ☐☐ ☐☐ (yyyy / mm / dd) |

CRU #044 TRIC VCI Plate #046 Phone Follow Up

**Subject ID:** [ ][ ] [ ][ ][ ] *Centre* *Subject ID*

**Date:** [ ][ ][ ][ ] [ ][ ] [ ][ ] *yyyy* *mm* *dd*

# DAY 2 PHONE VISIT

| | | |
|---|---|---|
| 1. Subject contacted by phone on day 2 (if not reached, attempt to contact on each of days 3-6): | ☐ Yes | ☐ No |
| 2. Has the subject attempted to use the device: | ☐ Yes | ☐ No |
| 3. Does the subject report any problems with using the device: | ☐ Yes | ☐ No |
| 4. Is the subject willing to continue to participate in the study: | ☐ Yes | ☐ No |

| 5. Complete the visit checklist: | |
|---|---|
| Review device instructions | ☐ |
| Review diary instructions | ☐ |

**COMMENTS** (optional)

Signature: _____ Date: [ ][ ][ ][ ] [ ][ ] [ ][ ] *yyyy* *mm* *dd*

CRU #044 TRIC VCI Plate #047 Phone Follow Up

**Subject ID:** ☐☐ ☐☐☐ *Centre* *Subject ID*

**Date:** ☐☐☐☐ ☐☐ ☐☐ *yyyy* *mm* *dd*

# DAY 15 PHONE VISIT

| | | |
|---|---|---|
| 1. Subject contacted by phone on day 15 (if not reached, attempt to contact on each of days 16-19): | ☐ Yes | ☐ No |
| 2. Has the subject attempted to use the device: | ☐ Yes | ☐ No |
| 3. Does the subject report any problems with using the device: | ☐ Yes | ☐ No |
| 4. Is the subject willing to continue to participate in the study: | ☐ Yes | ☐ No |

| 5. Complete the visit checklist: | |
|---|---|
| Review device instructions | ☐ |
| Review diary instructions | ☐ |

**COMMENTS** (optional)

Signature: _____ Date: ☐☐☐☐ ☐☐ ☐☐ *yyyy* *mm* *dd*

CRU #044 TRIC VCI Plate #048 Follow Up

**Subject ID:** Centre Subject ID **Date:** y y y y m m d d

# DAY 30 VISIT *(page 1 of 2)*

| MEDICAL HISTORY | | |
|---|---|---|
| 1. History of new prior transient ischemic attack since randomization? | ☐ Yes | ☐ No |
| If yes, then complete 1.a. and 1.b. | | |
| 1.a. Is there a history of more than one new ischemic attack? | ☐ Yes | ☐ No |
| 1.b. What was the date of the most recent prior transient attack? Date: y y y y m m d d | | |
| 2. History of new ischemic stroke since randomization: | ☐ Yes | ☐ No |
| If yes, then complete 2.a and 2.b. | | |
| 2.a. Is there a history of more than one new ischemic stroke? | ☐ Yes | ☐ No |
| 2.b. What was the date of the most recent ischemic stroke? Date: y y y y m m d d | | |
| 3. History of new intracerebral hemorrhage since randomization: | ☐ Yes | ☐ No |
| If yes, then complete 3.a and 3.b. | | |
| 3.a. Is there a history of more than one new intracerebral hemorrhages? | ☐ Yes | ☐ No |
| 3.b. What was the date of the most recent intracerebral hemorrhage? Date: y y y y m m d d | | |
| 4. History of new stroke of unknown type since randomization: | ☐ Yes | ☐ No |
| If yes, then complete 4.a and 4.b. | | |
| 4.a. Is there a history of more than one new stroke of unknown type? | ☐ Yes | ☐ No |
| 4.b. What was the date of the most recent stroke of unknown type? Date: y y y y m m d d | | |

CRU #044 TRIC VCI Plate #049 Follow Up

**Subject ID:** Centre Subject ID **Date:** y y y y m m d d

# DAY 30 VISIT *(page 2 of 2)*

| Day 30 visit checklist | |
|---|---|
| Retrieve device | ☐ |
| Retrieve patient diary | ☐ |

Signature: _____ Date: y y y y m m d d

CRU #044 TRIC VCI Plate #050 End

**Subject ID:** [ ][ ] [ ][ ][ ] *Centre* *Subject ID*

**Date:** [ ][ ][ ][ ] [ ][ ] [ ][ ] *y y y y* *m m* *d d*

# DAY 90 VISIT

## MEDICAL HISTORY

1. History of new prior transient ischemic attack since randomization? ☐ Yes ☐ No

If yes, then complete 1.a. and 1.b.

1.a. Is there a history of more than one new ischemic attack? ☐ Yes ☐ No

1.b. What was the date of the most recent prior transient attack?

Date: [ ][ ][ ][ ] [ ][ ] [ ][ ] *y y y y* *m m* *d d*

2. History of new ischemic stroke since randomization: ☐ Yes ☐ No

If yes, then complete 2.a and 2.b.

2.a. Is there a history of more than one new ischemic stroke? ☐ Yes ☐ No

2.b. What was the date of the most recent ischemic stroke?

Date: [ ][ ][ ][ ] [ ][ ] [ ][ ] *y y y y* *m m* *d d*

3. History of new intracerebral hemorrhage since randomization: ☐ Yes ☐ No

If yes, then complete 3.a and 3.b.

3.a. Is there a history of more than one new intracerebral hemorrhages? ☐ Yes ☐ No

3.b. What was the date of the most recent intracerebral hemorrhage?

Date: [ ][ ][ ][ ] [ ][ ] [ ][ ] *y y y y* *m m* *d d*

4. History of new stroke of unknown type since randomization: ☐ Yes ☐ No

If yes, then complete 4.a and 4.b.

4.a. Is there a history of more than one new stroke of unknown type? ☐ Yes ☐ No

4.b. What was the date of the most recent stroke of unknown type?

Date: [ ][ ][ ][ ] [ ][ ] [ ][ ] *y y y y* *m m* *d d*

CRU #044 TRIC VCI Plate #051

☐ Randomization ☐ End
☐ Follow Up

**Subject ID:** ☐☐ ☐☐☐ *Centre* *Subject ID*

**Date:** ☐☐☐☐ ☐☐ ☐☐ *yyyy* *mm* *dd*

## COGNITIVE SCORES *(page 1 of 2)*

| | |
|---|---|
| Trail-making part A completed: | ☐ Yes ☐ No ☐ Other:_____ |
| Trail-making part A time to completion (seconds): | ☐☐☐ |
| Trail-making part B completed: | ☐ Yes ☐ No ☐ Other:_____ |
| Trail-making part B time to completion (seconds): | ☐☐☐ |
| 10-item word list learning completed: | ☐ Yes ☐ No ☐ Other:_____ |
| Trial 1 immediate recall: | ☐☐ |
| Trial 1 intrusions: | ☐☐ |
| Trial 2 immediate recall: | ☐☐ |
| Trial 2 intrusions: | ☐☐ |
| Trial 3 immediate recall: | ☐☐ |
| Trial 3 intrusions: | ☐☐ |
| Letter A fluency completed: | ☐ Yes ☐ No ☐ Other:_____ |
| Letter A fluency number of words: | ☐☐ |
| Letter S fluency completed: | ☐ Yes ☐ No ☐ Other:_____ |
| Letter S fluency number of words: | ☐☐ |
| Animal fluency completed: | ☐ Yes ☐ No ☐ Other:_____ |
| Animal fluency number of words: | ☐☐ |

CRU #044 TRIC VCI Plate #052

☐ Randomization ☐ End
☐ Follow Up

**Subject ID:** ☐☐ ☐☐☐ (Centre / Subject ID)

**Date:** ☐☐☐☐ ☐☐ ☐☐ (yyyy / mm / dd)

## COGNITIVE SCORES *(page 2 of 2)*

| | | | |
|---|---|---|---|
| Vegetable fluency completed: | ☐ Yes | ☐ No | ☐ Other:_____ |
| Vegetable fluency number of words: | ☐☐ | | |

| | | | |
|---|---|---|---|
| 10-item word list delayed recall completed: | ☐ Yes | ☐ No | ☐ Other:_____ |
| Delayed recall correct: | ☐☐ | | |
| Delayed recall intrusions: | ☐☐ | | |

Signature: _____ Date: ☐☐☐☐ ☐☐ ☐☐ (yyyy / mm / dd)

CRU #044 TRIC VCI Plate #053

☐ Randomization ☐ End
☐ Follow Up

**Subject ID:** ☐☐ ☐☐☐ (Centre / Subject ID)

**Date:** ☐☐☐☐ ☐☐ ☐☐ (yyyy / mm / dd)

# MRI TRANSMITTAL

| | |
|---|---|
| Date of MRI: | ☐☐☐☐ ☐☐ ☐☐ (yyyy / mm / dd) |
| MRI transmitted: | ☐ Yes ☐ No |

If no, give reason:

- ☐ No longer participating in the study (study termination CRF should also have been completed)
- ☐ Participant declined
- ☐ Not completed due to claustrophobia
- ☐ MRI contraindication
- ☐ MRI technical problem
- ☐ Other reason:_____

Signature:_____ Date: ☐☐☐☐ ☐☐ ☐☐ (yyyy / mm / dd)

CRU #044 TRIC VCI Plate #054 End

**Subject ID:** ☐☐ ☐☐☐ (Centre / Subject ID) **Date:** ☐☐☐☐ ☐☐ ☐☐ (yyyy / mm / dd)

# STUDY TERMINATION

| Subject has ceased to participate in TRIC VCI: | ☐ Yes |
|---|---|

**Please indicate reason:**

**Subject Adherence**

- ☐ No device sessions for three or more consecutive days
- ☐ Declined to continue because of device-related discomfort
- ☐ Declined to continue for other reasons

Indicate reason: _____

**Contraindications to RIC**

- ☐ Diagnosed with deep venous thrombosis of the upper or lower extremity, or other deep veins
- ☐ Upper arm skin breakdown or rash
- ☐ Arm surgery
- ☐ Initiated treatment with anticoagulant
- ☐ Poorly controlled blood pressure (mean values greater than 180 mmHg systolic)
- ☐ Other physician-determined contraindication to continuing treatment with RIC

Indicate the condition: _____

**Medical Comorbidities**

- ☐ New medical condition that in the judgement of the site physician precludes continued participation in the trial

Indicate the new medical condition:_____

☐ Died ☐☐☐☐ ☐☐ ☐☐ (yyyy / mm / dd)

*Signature of investigator confirms the Study Termination :* _____

***e-signature***
***iDataFax use only***

☐☐ : ☐☐ ☐☐☐☐ ☐☐ ☐☐ (hh : mm yyyy mm dd)

PI's printed first and last name: _____

CRU #044 TRIC VCI Plate #055

Pg#:

**Subject ID:** Centre Subject ID

**Date:** yyyy mm dd

# ADVERSE EVENTS

| | | | |
|---|---|---|---|
| AE Event # | Adverse Event term _____ | | |
| AE Start Date: | yyyy mm dd | | |
| AE End Date (or Continuing): | yyyy mm dd<br>Continuing | | |
| Outcome: | Fatal | Not recovered/ not resolved | Recovered w/sequelae |
| | Recovered w/o sequelae | Recovering/ resolving | |
| Severity/Grade: | Mild | Moderate | Severe |
| Is the Event Serious? | Yes (Complete SAE) | No | |
| Is the Event Expected? | Yes | No | |
| AE Treatment: | None | Medication(s) | Non-medication TX |
| Action Taken with Study Intervention: | None | Interrupted | Discontinued |
| | Device sessions reduced | Device sessions increased | Not Applicable |
| Attribution/Relatedness: | Definite | Probable | Possible |
| | Unlikely | Unrelated | |

CRU #044 TRIC VCI Plate #056

Pg#:

**Subject ID:** Centre Subject ID

**Date:** yyyy mm dd

# MedDRA CODING FOR ADVERSE EVENT (AE)

***(to be completed by coordinating site)***

| AE Event # | Site Adverse Event term |
|---|---|
| | Common sense Adverse Event term |
| AE Category:<br><br>(Please look up corresponding AE Category at :https://safetyprofiler-ctep.nci.nih.gov/) | |

| | Term | Code |
|---|---|---|
| System Organ Classes (SOC) | | |
| High Level Group Term (HLGT) | | |
| High Level Term (HLT) | | |
| Preferred Term (PT) | | |
| Lowest Level Term (LLT) | | |

CRU #044 TRIC VCI Plate #057

Pg#:

**Subject ID:** Centre Subject ID

**Date:** y y y y m m d d

# SERIOUS ADVERSE EVENTS (SAE) *(page 1 of 2)*

| | |
|---|---|
| SAE Event # | Serious Adverse Event term _____ |
| Report Type | ☐ Initial Report<br>☐ Follow-up Report F/U Report #<br>☐ Final Report |
| SAE Classification: | ☐ Fatal (resulted in death) |
| | ☐ A life-threatening occurrence |
| | ☐ Requires inpatient hospitalization or prolongation of existing hospitalization |
| | ☐ Results in persistent or significant disability/incapacity |
| | ☐ Results in congenital anomaly/birth defect |
| | ☐ A significant medical incident that, based upon appropriate medical judgment, may jeopardize the subject and require medical or surgical intervention to prevent one of the outcomes listed above. |
| | ☐ Loss of confidentiality that results in criminal or civil liability for participation or damage to financial standing, employability, insurability or reputation of the participant |
| SAE Start Date: | y y y y m m d d |
| SAE End Date (or Continuing): | y y y y m m d d<br>☐ Continuing |
| Grade: | ☐ Mild ☐ Moderate ☐ Severe<br>☐ Life Threatening ☐ Death (Fatal) |
| Is the Event Expected? | ☐ Yes ☐ No |

CRU #044 TRIC VCI Plate #058

Pg#:

**Subject ID:** Centre Subject ID

**Date:** yyyy mm dd

# SERIOUS ADVERSE EVENTS (SAE) *(page 2 of 2)*

| | |
|---|---|
| Attribution/Relatedness: | ☐ Definite ☐ Probable ☐ Possible ☐ Unlikely ☐ Unrelated |
| Outcome: | ☐ Fatal ☐ Not recovered/ not resolved ☐ Recovered w/sequelae ☐ Recovered w/o sequelae ☐ Recovering/ resolving |
| Lead Site Notified Date: | yyyy mm dd |
| Local IRB/REB Notified Date: | yyyy mm dd |
| Narrative/Details: | _____ |

*Signature of investigator confirms the reported SAE :* _____

***e-signature***
***iDataFax use only***

hh : mm yyyy mm dd

PI's printed first and last name: _____

CRU #044 TRIC VCI Plate #059

Pg#:

**Subject ID:** Centre Subject ID

**Date:** yyyy mm dd

# SAFETY ADJUDICATION (SAE)

## REPORT INFORMATION

| | |
|---|---|
| Serious Adverse Event Name | _____ |
| SAE Start Date | yyyy mm dd |
| SAE End Date (or Continuing): | yyyy mm dd ☐ Continuing |
| Report Type | ☐ Initial Report ☐ Follow-up Report F/U Report # ☐ ☐ Final Report |
| Outcome | ☐ Fatal ☐ Not recovered/ not resolved ☐ Recovered w/sequelae ☐ Recovered w/o sequelae ☐ Recovering/ resolving |

## Is the Event

| | | |
|---|---|---|
| **Serious**? | ☐ Yes | ☐ No |
| Probably or definitely **Related** to the study device? | ☐ Yes | ☐ No |
| Is the event **expected**? | ☐ Yes | ☐ No |

## COMMENTS *(optional)*

Adjudication done by: _____
*(Print Name)*

CRU #044 TRIC VCI Plate #060

Pg#:

**Subject ID:** Centre Subject ID

**Date:** yyyy mm dd

# PROTOCOL DEVIATION

- ☐ Randomization Error
- ☐ Missed follow up visit:
- ☐ Follow up visit occurred outside of study window
- ☐ Incomplete follow up visit?
- ☐ Other: _____

Details:

_____

_____

_____

CRU #044 TRIC VCI Plate #061

Pg#:

**Subject ID:** Centre Subject ID

**Date:** yyyy mm dd

# PROTOCOL VIOLATION

- ☐ Enrolment does not comply with Inclusion Criteria
- ☐ Enrolment does not comply with Exclusion Criteria
- ☐ Failure to obtain Informed Consent
- ☐ Failure to report a Serious Adverse Event to the local IRB/REB and Sponsor
- ☐ Improper breaking of the blind
- ☐ Failure to report unanticipated problem involving the risks to participants or others to the IRB/REB and Sponsor
- ☐ Participant stopped treatment early
- ☐ Other: _____

CRU #044 TRIC VCI Plate #062

Pg#:

**Subject ID:** Centre Subject ID

**Date:** yyyy mm dd

# MEDICATIONS LIST

Medication list (list all, including any antiplatelet drugs with dose and frequency

Medication Name: _____

Indication: _____

Dose: . 

Units: ☐ mg ☐ mcg ☐ mL ☐ cc ☐ IU ☐ mEq ☐ oz ☐ tsp ☐ tbl ☐ gtt

Route: ☐ po ☐ pr ☐ sub-q ☐ sub-lingual ☐ IM ☐ IV ☐ Patch ☐ Topical ☐ Nasal ☐ Other: _____

Frequency: ☐ OD ☐ BID ☐ TID ☐ QID ☐ PRN ☐ Other: _____

Start Date: yyyy mm dd

End Date: yyyy mm dd ***OR*** ☐ Unable to determine

Medication Name: _____

Indication: _____

Dose: . 

Units: ☐ mg ☐ mcg ☐ mL ☐ cc ☐ IU ☐ mEq ☐ oz ☐ tsp ☐ tbl ☐ gtt

Route: ☐ po ☐ pr ☐ sub-q ☐ sub-lingual ☐ IM ☐ IV ☐ Patch ☐ Topical ☐ Nasal ☐ Other: _____

Frequency: ☐ OD ☐ BID ☐ TID ☐ QID ☐ PRN ☐ Other: _____

Start Date: yyyy mm dd

End Date: yyyy mm dd ***OR*** ☐ Unable to determine

Signature: _____ Date: yyyy mm dd

CRU #044 TRIC VCI Plate #063 Randomization

**Subject ID:** ☐☐ (Centre) ☐☐☐ (Subject ID) **Date:** ☐☐☐☐ (yyyy) ☐☐ (mm) ☐☐ (dd)

# DEVICE PROVISION

| | | | |
|---|---|---|---|
| 1. Randomization and device provision checklist: | ☐ Subject randomized | | |
| | ☐ Device provided | | |
| | ☐ Device instructions provided | | |
| | ☐ Subject diary provided | | |
| | ☐ Device training provided | | |
| 2. First treatment cycle: | ☐ Completed | ☐ Not completed/not tolerated | |
| **If not completed, then subject will not continue in the study. Complete CRF Study Drop Out.** | | | |
| 3.Treatment-related discomfort: Show the Numeric Pain Rating Scale/Wong-Baker FACES Pain Rating Scale to the subject, instruct the subject on how to use it, and record: | | | |
| | 3.a. MAXIMUM pain during the treatment cycle: | ☐☐ [range 0-10] | |
| | 3.b. Pain level during the last cuff inflation of the cycle: | ☐☐ [range 0-10] | |
| 4. Symptoms reported during treatment (check all that apply): | | | |
| Was the treatment painful? | ☐ Yes | ☐ No | ☐ Not sure |
| Was there tingling (paresthesia)? | ☐ Yes | ☐ No | ☐ Not sure |
| 5. Other symptoms during treatment: | | | |
| _____ | | | |
| _____ | | | |
| 6. Is subject willing to continue in the study: | ☐ Yes | ☐ No | |
| **If "No", then subject will not continue in the study. Complete CRF Study Drop Out.** | | | |

Signature:_____ Date: ☐☐☐☐ (yyyy) ☐☐ (mm) ☐☐ (dd)

## SUPPLEMENTARY FILE 3: TRIC-VCI TRIAL MANAGEMENT

### Study coordination

The trial will be organized by an executive committee principally centred in Calgary at the Calgary Stroke Program (Hotchkiss Brain Institute, University of Calgary and Department of Clinical Neurosciences). The overall PI for the trial will be Eric Smith. The Financial and Contracts Manager will be Anna Charlton. The Clinical Nursing Coordinator will be Karyn Fischer. The safety of the trial will be overseen by an independent Data Safety and Monitoring Board (DSMB). A Steering Committee will manage the day-to-day activities of the trial. Data will be managed by the University of Calgary Clinical Research Unit. Neuroimaging data will be managed by the Calgary Image Processing and Analysis Center (CIPAC) of Alberta Health Services.

### Trial Steering Committee

The Steering Committee will consist of the trial co-investigators and will be chaired by the trial principal investigator. Decisions will be made primarily by consensus, but in the absence of consensus they will be made by majority vote with the Chair serving as tie-breaker in case of tie votes. The Financial and Contracts Manager and Clinical Nursing Coordinator will attend Steering Committee meetings as non-voting members. Steering Committee teleconferences will be held no less frequently than once per quarter.

### Publications Committee

The Steering Committee will also act as the publications committee. Steering Committee members will be invited to contribute as coauthors on study papers. All authors must meet International Committee of Medical Journal Editor criteria for authorship. Proposals for ancillary papers will be reviewed and approved by the Steering Committee.

### Data processing

All imaging, evaluation forms, reports, and other records that leave the site are identified only by the site and subject number to maintain subject confidentiality. All records are kept in a locked file cabinet. Clinical information is not released without written permission of the subject, except as necessary for monitoring by IRB/REB, Health Canada, the sponsor, or the sponsor's designee.

All study investigators at the clinical sites must ensure that the confidentiality of personal identity and all personal medical information of study participants are maintained at all times. Federal legislation in Canada (Personal Information Protection and Electronic Documents Act – PIPEDA), and provincial legislation (eg. Health Information Act – HIA in Alberta) where applicable, must be followed. Additionally, any U.S. clinical sites must follow privacy obligations to study participants under the Health Insurance Portability and Accountability Act (HIPAA). European or Asian/Australasian sites must conform to local privacy and confidentiality law and custom. On the CRFs and other study documents or image materials submitted to the CRU, the subjects are identified only by study identification code.

Personal medical information may be reviewed for the purpose of verifying data recorded in the CRF by the site monitors. Other properly authorized persons, such as the regulatory authorities, may also have access to these records. Personal medical information is always treated as confidential.

**Audit and inspection**

The Sponsor-Investigator and any Participating Site Investigators should understand that source documents for this trial should be made available to appropriately qualified personnel from the Sponsor-Investigator or designee after appropriate notification. The verification of the CRF data must be by direct inspection of source documents.

Any Participating Site Investigators shall supply the Sponsor-Investigator on request with any required background data from the study documentation or clinic records. This is particularly important when CRFs are illegible or when errors in data transcription are suspected. In case of special problems and/or governmental queries or requests for audit inspections, it is also necessary to have access to the complete study records, provided that subject confidentiality is protected.

**Archiving**

The Sponsor-Investigator (and any Participating Site Investigators) must keep both (1) Investigator's Study Files and (2) subject clinical source documents on file according to local clinical trial regulation. For example, at the University of Calgary, for non-Health Canada regulated studies, that period is 5 years from the time of official closure of the study. After that period of time the documents may be destroyed, subject to local regulations.

Data sharing policies will follow the spirit of the National Institute of Health (NIH) policy [http://grants2.nih.gov/grants/policy/data_sharing/data_sharing_guidance.htm]. A similar policy is in place at the Canadian Institutes of Health Research (CIHR). In addition, the Executive Committee will follow the CIHR guidelines on public access to trial results and make the results available as free-access using PubMed. Upon completion of the trial, a public use database will be prepared by stripping any and all personal identifiers. The public use database, consisting of several data files, should contain: (1) baseline and demographic characteristics; (2) outcomes assessments; (3) MRI data; (4) cognitive data; (5) concomitant medications; and (6) adverse events. Each data file is made available as a formatted text file or other electronic format. The data files are distributed along with the data dictionary and a brief instruction ("Readme") file. These data files will be made available to the public one year after completion of follow-up for the last subject.

SPIRIT

STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

| Section/item | Item No | Description | Addressed on page number |
|---|---|---|---|
| **Administrative information** | | | |
| Title | 1 | Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym | 1 |
| Trial registration | 2a | Trial identifier and registry name. If not yet registered, name of intended registry | 8 |
| | 2b | All items from the World Health Organization Trial Registration Data Set | N/A |
| Protocol version | 3 | Date and version identifier | 8 |
| Funding | 4 | Sources and types of financial, material, and other support | 27 |
| Roles and responsibilities | 5a | Names, affiliations, and roles of protocol contributors | 1, 27 |
| | 5b | Name and contact information for the trial sponsor | 1 |
| | 5c | Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities | 27 |
| | 5d | Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee) | Supplement 5 |

**Introduction**

| | | | |
|---|---|---|---|
| Background and rationale | 6a | Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention | 5-7 |
| | 6b | Explanation for choice of comparators | 7 |
| Objectives | 7 | Specific objectives or hypotheses | 7 |
| Trial design | 8 | Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory) | 8 |

**Methods: Participants, interventions, and outcomes**

| | | | |
|---|---|---|---|
| Study setting | 9 | Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained | 13 |
| Eligibility criteria | 10 | Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists) | 10 |
| Interventions | 11a | Interventions for each group with sufficient detail to allow replication, including how and when they will be administered | 8-9 |
| | 11b | Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease) | 9 |
| | 11c | Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests) | 11 |
| | 11d | Relevant concomitant care and interventions that are permitted or prohibited during the trial | 10 |
| Outcomes | 12 | Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended | 12 |
| Participant timeline | 13 | Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure) | 12 |

| | | | |
|---|---|---|---|
| Sample size | 14 | Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations | 12 |
| Recruitment | 15 | Strategies for achieving adequate participant enrolment to reach target sample size | 12 |
| **Methods: Assignment of interventions (for controlled trials)** | | | |
| Allocation: | | | |
| Sequence generation | 16a | Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions | 9 |
| Allocation concealment mechanism | 16b | Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned | 9 |
| Implementation | 16c | Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions | 16 |
| Blinding (masking) | 17a | Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how | 9 |
| | 17b | If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial | 9 |
| **Methods: Data collection, management, and analysis** | | | |
| Data collection methods | 18a | Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol | 10-11, Supplement 2 |
| | 18b | Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols | 12 |

| | | | |
|---|---|---|---|
| Data management | 19 | Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol | 16, supplement 5 |
| Statistical methods | 20a | Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol | 14 |
| | 20b | Methods for any additional analyses (eg, subgroup and adjusted analyses) | 14 |
| | 20c | Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation) | 15 |
| **Methods: Monitoring** | | | |
| Data monitoring | 21a | Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed | 14, supplement 5 |
| | 21b | Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial | not applicable |
| Harms | 22 | Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct | 18 |
| Auditing | 23 | Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor | 17 |
| **Ethics and dissemination** | | | |
| Research ethics approval | 24 | Plans for seeking research ethics committee/institutional review board (REC/IRB) approval | 16 |
| Protocol amendments | 25 | Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators) | 16 |

| | | | |
|---|---|---|---|
| Consent or assent | 26a | Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32) | _____16_____ |
| | 26b | Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable | _____16_____ |
| Confidentiality | 27 | How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial | _____16_____ |
| Declaration of interests | 28 | Financial and other competing interests for principal investigators for the overall trial and each study site | _____16_____ |
| Access to data | 29 | Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators | _____16_____ |
| Ancillary and post-trial care | 30 | Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation | _not applicable_ |
| Dissemination policy | 31a | Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions | _____18_____ |
| | 31b | Authorship eligibility guidelines and any intended use of professional writers | _supplement 5 |
| | 31c | Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code | _____18_____ |
| **Appendices** | | | |
| Informed consent materials | 32 | Model consent form and other related documentation given to participants and authorised surrogates | _supplement 4 |
| Biological specimens | 33 | Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable | _supplement 2 |

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.