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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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3 **Trial of Remote Ischaemic Pre-Conditioning in Vascular Cognitive Impairment (TRIC-VCI):**
4 **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 consist 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 $\geq 80\%$ 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.

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Registration Details: NCT04109963; Pre-results

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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

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3 biomarkers of RIC. Candidate biomarkers include circulating nitrite, heat shock protein 27 (HSP-
4 27), microRNA-144, and interleukin-10.¹³⁻¹⁶
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10 In a bilateral carotid occlusion model of VCI in mice, chronic daily RIC demonstrated increased
11 angiogenesis (capillary density), cerebral flood flow, and preservation of white matter
12 myelination at 1-month and 4-months.¹⁷ In humans, RIC has been trialled for percutaneous
13 coronary intervention (PCI) in the setting of acute myocardial infarction,^{18 19} elective PCI,¹⁹ and
14 cardiac surgery.²⁰ RIC has also been studied in the past few years in cerebrovascular disease,
15 mostly applied to the upper-limb but some in the lower-limb,²¹⁻²⁶ and in several studies of peri-
16 /post-conditioning (happening after ischaemic/haemorrhagic injury).²⁷⁻²⁹ Bilateral upper-limb RIC
17 protects against recurrent stroke in intracranial arterial stenosis.²² A systematic review of RIC
18 included three trials (371 participants) for ischaemic stroke prevention and four trials (364
19 participants) for ischaemic stroke treatment, and found low-quality evidence that RIC reduces
20 recurrent stroke risk in patients with intracerebral artery stenosis and reduces stroke severity in
21 patients undergoing carotid stenting.³⁰ There is also preliminary evidence of efficacy for this
22 therapy in cSVD. A trial of 17 patients with cSVD randomised to RIC or sham-RIC reported
23 improved mean flow velocity of the middle cerebral artery, lower dizziness handicap inventory
24 score, and lower post-treatment WMH volume in the RIC group.²³ A trial in 36 patients with
25 cSVD reported a significant reduction in WMH volume at 1-year compared to sham-RIC and a
26 significant difference on visuospatial and executive function sections of the Montreal Cognitive
27 Assessment (MoCA), though there was no significant change in the number of lacunes.²⁴
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50 Prior studies of RIC in cSVD have been small and essentially hypothesis-generating, and
51 several uncertainties remain. First, the required “dose” of RIC sessions to observe a favourable
52 effect is uncertain: a number of published studies have used bilateral upper-arm RIC twice
53 daily,^{22 24} but if similar results are obtained with once-daily and/or single upper-arm sessions,
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3 this would be especially appealing for patients and facilitate treatment adoption. Importantly,
4 human³¹ and animal model^{32 33} studies show that single limb RIC with only 3-4 cycles can
5 reduce end organ ischaemic damage. The most comprehensive dose-finding study³³ found that
6 more than one limb, more than four cycles, and more than 5-minutes of ischaemia conferred no
7 additional reductions in infarct size in a mouse model of acute myocardial infarction. Second,
8 most of the published studies have reported an exceptionally high rate of patient compliance
9 (>80%), even with bilateral upper-arm, twice-daily sessions – requiring at least 100 minutes
10 daily, during which they can do little meaningful activity. It is uncertain whether similarly high
11 rates of compliance can be expected in the trial target population of persons with objective
12 evidence of cognitive impairment. Third, the persistence of treatment effects beyond the
13 cessation of RIC – as suggested by the “late phase” of RIC-related physiological changes
14 suggested by laboratory studies¹⁷ – remains to be demonstrated. The aforementioned mouse
15 model of bilateral carotid occlusion showed similar efficacy of RIC in mice receiving 1-month or
16 4-months of therapy,¹⁷ but it is unclear if such persistence can be seen in humans. Fifth, prior
17 cSVD trials (including of non-RIC treatments) have suffered from common methodological
18 problems including a lack of neuroimaging for diagnosis and classification, low quality trial
19 design (lack of intent-to-treat analysis or pre-specified primary outcomes, failure to account for
20 multiple comparisons), and lack of use of biomarkers for monitoring and treatment response.³⁴
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43 Therefore, we propose an early phase trial to lay the foundation for a research program to
44 further investigate the effect of RIC on prevention of cognitive decline caused by brain infarction
45 from cSVD. We will examine whether different doses of daily RIC performed for 1-month are
46 tolerable and safe, whether they result in improved cerebral blood flow, and whether the
47 biomarker effects of 1-month of treatment are sustained at 3-months.
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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

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3 randomisation visit (to determine whether the participant is eligible to be randomised based on
4 adherence during the run-in period) and 30-day visits. The proportion that complete the run-in
5 period will be a secondary endpoint.
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10 11 **Discontinuation from study treatment**

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

- 14 1. Patient declares unwillingness to proceed with the intervention.
- 15 2. Treatment is interrupted for >48 hours for any reason.
- 16 3. Diagnosis of deep venous thrombosis (DVT) or pulmonary embolism.
- 17 4. Surgery on the upper extremity is performed or clinically indicated prior to cessation of
18 the 30-day active treatment period.
- 19 5. Initiation of anticoagulation is clinically indicated.
- 20 6. Patient develops any other serious adverse event deemed by the attending physician to
21 merit cessation of RIC.
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32 The time-point of discontinuation will be recorded as accurately as possible (using the device
33 data) to determine the total number of actual treatment days for each patient. All patients will be
34 followed to the end of the study period and analyzed in their assigned treatment arm.
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41 **Randomisation scheme**

42 All subjects will be enrolled in this study consecutively and randomised into the two treatment
43 groups in a 1:1 ratio. Randomisation will be conducted using a web-based algorithm with
44 treatment assignment allocated by web-based real-time interaction with the site. Treatment
45 assignments will be made using the Permuted Blocks method with randomly selected block
46 sizes of 2, 4, or 6.
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56 **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 (> 10 mm 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 learning⁴⁰ 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 $\geq 80\%$ adherence) then we can predict with 95% confidence that the true adherence

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3 rate is 52% to 98%. This would provide enough confidence to proceed to a subsequent phase 2
4 study with a randomised sham control.
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9 Sample size calculations for biomarker efficacy are based on the ability to restore more normal
10 gray matter CBF in patients with VCI due to cSVD. Prior literature on CBF measurements in
11 cSVD has recently been systematically reviewed⁴². Based on a prior study of cSVD VCI
12 patients,⁴³ we estimate gray matter CBF will be 37.8 ± 12.4 mL/100g brain tissue/minute in cSVD
13 and 55.8 ± 12.4 mL/100g/minute in age matched healthy controls. We estimate that RIC will
14 restore 52% of normal CBF (i.e. an increase to 46.8 mL/100g/minute), as seen in an animal
15 model of VCI¹⁷. CBF can be measured with good precision using MRI PCASL (estimated within-
16 subject coefficient of variation 4.1% based on two studies^{44 45}). Based on these assumptions
17 and two-tailed $\alpha=0.05$, the current trial will provide >99% power to detect a mean increase
18 of 9 mL/100g/min CBF from baseline within each arm. For a future phase 2b study, a sample
19 size of 32 in each arm would provide 80% power and a sample size of 42 in each arm would
20 provide 90% power to determine whether RIC increases CBF by 9 mL/100g/minute compared to
21 a sham control.
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39 **Recruitment strategy and projected recruitment rate**

40 Patients will be screened at specialty Stroke/TIA clinics and Cognitive clinics (generally staffed
41 by neurologists, geriatricians, or psychiatrists) at each of the study sites. The initial screening
42 can be done by clinicians as part of usual care, since a number of the evaluations needed to
43 determine study eligibility (clinical history of cognitive symptoms, MoCA, and neuroimaging) are
44 commonly used clinical tests recommended by Canadian clinical guidelines. We aim for a
45 recruitment rate of 1 patient per month per site (5 per month across all sites), aiming to achieve
46 our target sample size of 24 in 7-8 months.
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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 $\geq 80\%$ 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

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3 Baseline characteristics and treatment assignments of patients with and without missing data
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5 will be compared to identify any significant differences that might affect the interpretation of
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7 results. Given the relatively small sample size, we will not perform multiple imputation on
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9 missing data.
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11 12 13 **Subgroup analyses**

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15 A priori subgroup analyses will include assessing tolerability and treatment effects by age, sex,
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17 self-reported physical activity level, and baseline burden of SVD.
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20 21 22 **Patient and public involvement**

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

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3 The Investigator's Study File will contain the protocol/amendments, Case Report and Query
4 Forms, IEC/IRB/governmental approval with correspondence, all versions of ethics approved
5 informed consent forms, staff curriculum vitae and authorization forms and other appropriate
6 documents/correspondence.
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13 Subject clinical source documents would include subject hospital/clinic records, physician's and
14 nurse's notes, appointment book, original laboratory reports, imaging reports, completed case
15 report forms (CRFs) (Supplementary File 4), any relevant pathology and special assessment
16 reports, signed ICFs, consultant letters, and subject screening and enrolment logs.
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24 For each subject enrolled, a CRF will be completed and signed by the Sponsor-Investigator
25 (and any Participating Site Investigator) or authorized delegate from the study staff. This
26 also applies to records for those patients who fail to complete the study (even during a pre--
27 randomisation screening period if a CRF was initiated). If a subject withdraws from the
28 study, the reason must be noted on a CRF. If a subject is withdrawn from the study because
29 of a treatment-limiting AE, thorough efforts will be made to clearly document the outcome.
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39 **Monitoring**

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41 All data will be monitored centrally by the coordinating center at the University of Calgary for
42 accuracy and completeness. The initial performance-monitoring assessment will take place after
43 the initial subject is enrolled, and the next monitoring assessment will take place at close out.
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47 The close-out monitoring assessment will take place at the completion of subject enrolment and
48 protocol required follow-up visits at the performance site. Monitoring visits will be done remotely
49 by teleconference, but the coordinating center reserves the right to conduct on site monitoring at
50 its discretion. The monitor will verify the adequacy of site facilities and staff, site recruitment,
51 subject randomisation, documentation of informed consent, and the presence of regulatory
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3 documents. During the monitoring visit, any omissions/corrections to data submitted to the
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5 database are noted and queries are generated by the monitor. At close out, sites are instructed
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7 in the record retention of all trial documents. Principal Investigators will issue a final report to the
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9 ethics board.
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13 Details on study coordination, the steering committee, data processing, audit and inspection,
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15 and archiving protocols are presented in **Supplementary File 5**.
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18 19 20 **Safety and Adverse Events**

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22 Adverse events should be reported as they occur on the CRF. Documentation must be
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24 supported by an entry in the subject's file. Each event should be described in detail along
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26 with start and stop dates, severity, relationship to the therapy as judged by the Investigator,
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28 action taken and outcome. Serious adverse events (SAEs) must be reported within 1
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30 business day of the local investigator or outcome assessor's first awareness of its
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32 occurrence. SAEs will be reviewed by the trial medical monitor. Because this is not a
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34 regulatory trial, SAEs do not require reporting to Health Canada or other regulatory
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36 authorities. Because the adverse event profile of RIC has been quite benign in previous
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38 trials, we do not predict that there will be unexpected SAEs.
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43 Safety outcomes of DVT and PE, arm neurovascular injury, and serious adverse events
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45 will be adjudicated by a medical monitor, an independent neurologist with experience in
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47 clinical trials, who will report these events to the Steering Committee.
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50 51 **Data dissemination**

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53 Results will be disseminated through peer-reviewed publications, professional organisations,
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55 and conferences. The de-identified study dataset and analysis code will be posted to the
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3 University of Calgary section of the PRISM dataverse at the time of publication of the main
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5 study results.
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9 The data from this trial will be used to inform decisions on study design for a subsequent phase
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11 2b trial including: 1) the frequency and intensity (one limb or two limbs) of RIC, based on
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13 adherence and safety data, 2) the choice of clinical cognitive and functional tests and
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15 assessment scales, based on feasibility and reliability, and 3) the choice of biomarkers, based
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17 on feasibility, reliability, and sensitivity to change over time.
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REFERENCES

1. Pantoni L. Cerebral small vessel disease: from pathogenesis and clinical characteristics to therapeutic challenges. *The Lancet Neurology* 2010;9(7):689-701. doi: 10.1016/S1474-4422(10)70104-6
2. Wardlaw JM, Smith EE, Biessels GJ, et al. Neuroimaging standards for research into small vessel disease and its contribution to ageing and neurodegeneration. *The Lancet Neurology* 2013;12(8):822-38. doi: 10.1016/S1474-4422(13)70124-8
3. Schneider JA, Arvanitakis Z, Bang W, et al. Mixed brain pathologies account for most dementia cases in community-dwelling older persons. *Neurology* 2007;69(24):2197-204. doi: 10.1212/01.wnl.0000271090.28148.24
4. Conklin J, Silver FL, Mikulis DJ, et al. Are acute infarcts the cause of leukoaraiosis? Brain mapping for 16 consecutive weeks. *Annals of neurology* 2014;76(6):899-904. doi: 10.1002/ana.24285
5. Kimberly WT, Gilson A, Rost NS, et al. Silent ischemic infarcts are associated with hemorrhage burden in cerebral amyloid angiopathy. *Neurology* 2009;72(14):1230-5. doi: 10.1212/01.wnl.0000345666.83318.03
6. Pavlovic AM, Pekmezovic T, Tomic G, et al. Baseline predictors of cognitive decline in patients with cerebral small vessel disease. *Journal of Alzheimer's disease : JAD* 2014;42 Suppl 3:S37-43. doi: 10.3233/JAD-132606
7. van der Flier WM, van Straaten EC, Barkhof F, et al. Small vessel disease and general cognitive function in nondisabled elderly: the LADIS study. *Stroke* 2005;36(10):2116-20. doi: 10.1161/01.STR.0000179092.59909.42
8. Smith EE, Saposnik G, Biessels GJ, et al. Prevention of Stroke in Patients With Silent Cerebrovascular Disease: A Scientific Statement for Healthcare Professionals From the American Heart Association/American Stroke Association. *Stroke* 2017;48(2):e44-e71. doi: 10.1161/STR.000000000000116

- 1
2
3 9. Jia J, Wei C, Liang J, et al. The effects of DL-3-n-butylphthalide in patients with vascular
4 cognitive impairment without dementia caused by subcortical ischemic small vessel
5 disease: A multicentre, randomized, double-blind, placebo-controlled trial. *Alzheimer's &*
6 *dementia : the journal of the Alzheimer's Association* 2016;12(2):89-99. doi:
7
8 10.1016/j.jalz.2015.04.010
9
10
11
12
13 10. Stokfisz K, Ledakowicz-Polak A, Zagorski M, et al. Ischaemic preconditioning - Current
14 knowledge and potential future applications after 30 years of experience. *Advances in*
15 *medical sciences* 2017;62(2):307-16. doi: 10.1016/j.advms.2016.11.006
16
17
18
19 11. Pan J, Li X, Peng Y. Remote ischemic conditioning for acute ischemic stroke: dawn in the
20 darkness. *Reviews in the neurosciences* 2016;27(5):501-10. doi: 10.1515/revneuro-
21
22 2015-0043
23
24
25 12. Berger MM, Macholz F, Mairbaurl H, et al. Remote ischemic preconditioning for prevention
26 of high-altitude diseases: fact or fiction? *Journal of applied physiology*
27
28 2015;119(10):1143-51. doi: 10.1152/jappphysiol.00156.2015
29
30
31 13. Hess DC, Blauenfeldt RA, Andersen G, et al. Remote ischaemic conditioning-a new
32 paradigm of self-protection in the brain. *Nature reviews Neurology* 2015;11(12):698-710.
33
34 doi: 10.1038/nrneurol.2015.223
35
36
37 14. Rassaf T, Totzeck M, Hendgen-Cotta UB, et al. Circulating nitrite contributes to
38 cardioprotection by remote ischemic preconditioning. *Circulation research*
39
40 2014;114(10):1601-10. doi: 10.1161/CIRCRESAHA.114.303822
41
42
43 15. Li J, Rohailla S, Gelber N, et al. MicroRNA-144 is a circulating effector of remote ischemic
44 preconditioning. *Basic research in cardiology* 2014;109(5):423. doi: 10.1007/s00395-
45
46 014-0423-z
47
48
49 16. Cai ZP, Parajuli N, Zheng X, et al. Remote ischemic preconditioning confers late protection
50 against myocardial ischemia-reperfusion injury in mice by upregulating interleukin-10.
51
52 *Basic research in cardiology* 2012;107(4):277. doi: 10.1007/s00395-012-0277-1
53
54
55
56
57
58
59

- 1
2
3 17. Khan MB, Hafez S, Hoda MN, et al. Chronic Remote Ischemic Conditioning Is
4 Cerebroprotective and Induces Vascular Remodeling in a VCID Model. *Translational*
5 *stroke research* 2018;9(1):51-63. doi: 10.1007/s12975-017-0555-1
6
7
8
9 18. McLeod SL, Iansavichene A, Cheskes S. Remote ischemic preconditioning to reduce
10 reperfusion injury during acute ST-segment-elevation myocardial infarction: A systematic
11 review and meta-analysis. *J Am Heart Assoc* 2017;6(5) doi: 10.1161/JAHA.117.005522
12
13
14 19. Blusztajn DI, Brooks MJ, Andrews DT. A systematic review and meta-analysis evaluating
15 ischemic conditioning during percutaneous coronary intervention. *Future Cardiol*
16 2017;13(6):579-92. doi: 10.2217/fca-2017-0042
17
18
19 20. Pierce B, Bole I, Patel V, et al. Clinical outcomes of remote ischemic preconditioning prior to
20 cardiac surgery: A meta-analysis of randomized controlled trials. *J Am Heart Assoc*
21 2017;6(2) doi: 10.1161/JAHA.116.004666
22
23
24 21. Meng R, Ding Y, Asmaro K, et al. Ischemic Conditioning Is Safe and Effective for Octo- and
25 Nonagenarians in Stroke Prevention and Treatment. *Neurotherapeutics : the journal of*
26 *the American Society for Experimental NeuroTherapeutics* 2015;12(3):667-77. doi:
27 10.1007/s13311-015-0358-6
28
29
30 22. Meng R, Asmaro K, Meng L, et al. Upper limb ischemic preconditioning prevents recurrent
31 stroke in intracranial arterial stenosis. *Neurology* 2012;79(18):1853-61. doi:
32 10.1212/WNL.0b013e318271f76a
33
34
35 23. Mi T, Yu F, Ji X, et al. The Interventional Effect of Remote Ischemic Preconditioning on
36 Cerebral Small Vessel Disease: A Pilot Randomized Clinical Trial. *European neurology*
37 2016;76(1-2):28-34. doi: 10.1159/000447536
38
39
40 24. Wang Y, Meng R, Song H, et al. Remote Ischemic Conditioning May Improve Outcomes of
41 Patients With Cerebral Small-Vessel Disease. *Stroke* 2017;48(11):3064-72. doi:
42 10.1161/STROKEAHA.117.017691
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
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2
3 25. Bilgin-Freiert A, Dusick JR, Stein NR, et al. Muscle microdialysis to confirm sublethal
4 ischemia in the induction of remote ischemic preconditioning. *Translational stroke*
5 *research* 2012;3(2):266-72. doi: 10.1007/s12975-012-0153-1
6
7
8
9
10 26. Zhao W, Meng R, Ma C, et al. Safety and Efficacy of Remote Ischemic Preconditioning in
11 Patients With Severe Carotid Artery Stenosis Before Carotid Artery Stenting: A Proof-of-
12 Concept, Randomized Controlled Trial. *Circulation* 2017;135(14):1325-35. doi:
13 10.1161/CIRCULATIONAHA.116.024807
14
15
16
17
18 27. Hougaard KD, Hjort N, Zeidler D, et al. Remote ischemic preconditioning as an adjunct
19 therapy to thrombolysis in patients with acute ischemic stroke: a randomized trial. *Stroke*
20 2014;45(1):159-67. doi: 10.1161/STROKEAHA.113.001346
21
22
23
24 28. England TJ, Hedstrom A, O'Sullivan S, et al. RECAST (Remote Ischemic Conditioning After
25 Stroke Trial): A Pilot Randomized Placebo Controlled Phase II Trial in Acute Ischemic
26 Stroke. *Stroke* 2017;48(5):1412-15. doi: 10.1161/STROKEAHA.116.016429
27
28
29
30 29. Koch S, Katsnelson M, Dong C, et al. Remote ischemic limb preconditioning after
31 subarachnoid hemorrhage: a phase Ib study of safety and feasibility. *Stroke*
32 2011;42(5):1387-91. doi: 10.1161/STROKEAHA.110.605840
33
34
35
36
37 30. Zhao W, Zhang J, Sadowsky MG, et al. Remote ischaemic conditioning for preventing and
38 treating ischaemic stroke. *Cochrane Database of Systematic Reviews* 2017(1)
39
40
41 31. Hildebrandt HA, Kreienkamp V, Gent S, et al. Kinetics and signal activation properties of
42 circulating factor(s) from healthy volunteers undergoing remote ischemic pre-
43 conditioning. *JACC Basic Transl Sci* 2016;1(1-2):3-13. doi: 10.1016/j.jacbts.2016.01.007
44
45
46
47 32. Pickard JM, Davidson SM, Hausenloy DJ, et al. Co-dependence of the neural and humoral
48 pathways in the mechanism of remote ischemic conditioning. *Basic Res Cardiol*
49 2016;111(4):50. doi: 10.1007/s00395-016-0568-z
50
51
52
53
54
55
56
57
58
59
60

- 1
2
3 33. Johnsen J, Pryds K, Salman R, et al. The remote ischemic preconditioning algorithm: effect
4 of number of cycles, cycle duration and effector organ mass on efficacy of protection.
5
6 *Basic Res Cardiol* 2016;111(2):10. doi: 10.1007/s00395-016-0529-6
7
8
9 34. Smith EE, Cieslak A, Barber P, et al. Therapeutic strategies and drug development for
10 vascular cognitive impairment. *J Am Heart Assoc* 2017;6(5):e005568. doi:
11
12 10.1161/JAHA.117.005568
13
14
15 35. Hansson L, Hedner T, Dahlof B. Prospective randomized open blinded end-point (PROBE)
16 study. A novel design for intervention trials. Prospective Randomized Open Blinded End-
17 Point. *Blood Press* 1992;1(2):113-9. [published Online First: 1992/08/01]
18
19
20 36. Nasreddine ZS, Phillips NA, Bedirian V, et al. The Montreal Cognitive Assessment, MoCA: a
21 brief screening tool for mild cognitive impairment. *Journal of the American Geriatrics*
22 *Society* 2005;53(4):695-9. doi: 10.1111/j.1532-5415.2005.53221.x [published Online
23
24
25
26
27
28
29
30
31 37. Reitan RM. Validity of the Trail Making Test as an indicator of organic brain damage.
32
33 *Percept Motor Skills* 1958;8:271-76.
34
35 38. Rosen W. Verbal fluency in aging and dementia. *J Clin Neuropsychol* 1980;2:135-46.
36
37 39. Barr A, Brandt J. Word-list generation deficits in dementia. *J Clin Exp Neuropsychol*
38
39 1996;18(6):810-22.
40
41 40. Mirra SS, Heyman A, McKeel D, et al. The Consortium to Establish a Registry for
42 Alzheimer's Disease (CERAD). Part II. Standardization of the neuropathologic
43 assessment of Alzheimer's disease. *Neurology* 1991;41(4):479-86. [published Online
44
45
46
47
48
49
50 41. Baykara E, Gesierich B, Adam R, et al. A novel imaging marker for small vessel disease
51 based on skeletonization of white matter tracts and diffusion histograms. *Annals of*
52 *neurology* 2016;80(4):581-92. doi: 10.1002/ana.24758
53
54
55
56
57
58
59
60

- 1
2
3 42. Shi Y, Thrippleton MJ, Makin SD, et al. Cerebral blood flow in small vessel disease: A
4
5 systematic review and meta-analysis. *Journal of cerebral blood flow and metabolism : official journal of the International Society of Cerebral Blood Flow and Metabolism*
6
7
8
9 2016;36(10):1653-67. doi: 10.1177/0271678X16662891
10
11 43. Schuff N, Matsumoto S, Kmiecik J, et al. Cerebral blood flow in ischemic vascular dementia
12
13 and Alzheimer's disease, measured by arterial spin-labeling magnetic resonance
14
15 imaging. *Alzheimer's & dementia : the journal of the Alzheimer's Association*
16
17 2009;5(6):454-62. doi: 10.1016/j.jalz.2009.04.1233
18
19 44. Chen Y, Wang DJ, Detre JA. Test-retest reliability of arterial spin labeling with common
20
21 labeling strategies. *Journal of magnetic resonance imaging : JMRI* 2011;33(4):940-9.
22
23 doi: 10.1002/jmri.22345
24
25 45. Wu B, Lou X, Wu X, et al. Intra- and interscanner reliability and reproducibility of 3D whole-
26
27 brain pseudo-continuous arterial spin-labeling MR perfusion at 3T. *Journal of magnetic*
28
29 *resonance imaging : JMRI* 2014;39(2):402-9. doi: 10.1002/jmri.24175
30
31 46. Wahlund LO, Barkhof F, Fazekas F, et al. A new rating scale for age-related white matter
32
33 changes applicable to MRI and CT. *Stroke* 2001;32(6):1318-22.
34
35 47. Galvin JE, Roe CM, Powlishta KK, et al. The AD8: a brief informant interview to detect
36
37 dementia. *Neurology* 2005;65(4):559-64. doi: 10.1212/01.wnl.0000172958.95282.2a
38
39 48. Bucks RS, Ashworth DL, Wilcock GK, et al. Assessment of activities of daily living in
40
41 dementia: development of the Bristol Activities of Daily Living Scale. *Age and ageing*
42
43 1996;25(2):113-20.
44
45 49. Ismail Z, Aguera-Ortiz L, Brodaty H, et al. The Mild Behavioral Impairment Checklist (MBI-
46
47 C): A Rating Scale for Neuropsychiatric Symptoms in Pre-Dementia Populations. *Journal*
48
49 *of Alzheimer's disease : JAD* 2017;56(3):929-38. doi: 10.3233/JAD-160979
50
51
52
53
54
55
56
57
58
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- 1
2
3 50. Ismail Z, Aguera-Ortiz L, Brodaty H, et al. The Mild Behavioral Impairment Checklist (MBI-
4
5 C): A rating scale for neuropsychiatric symptoms in pre-dementia populations. *Journal of*
6
7 *Alzheimer's disease* : JAD 2017;56(3):929-38. doi: 10.3233/JAD-160979
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For peer review only

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: 1. Beginning confluent WMH (ARWMC ⁴⁶ grade 2) on any slice on CT or MRI OR 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

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| 4 | 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. |
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| 6 | 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 |
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| 10 | 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 |
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| 13 | 11. Change in BADLS ⁴⁸ at 30--days and 90-days | Linear mixed model, testing difference at 30-days and 90-days |
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| 15 | 12. Difference in candidate blood biomarkers at 30-days and 90-days | Linear mixed model, testing difference at 30-days and 90-days |
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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

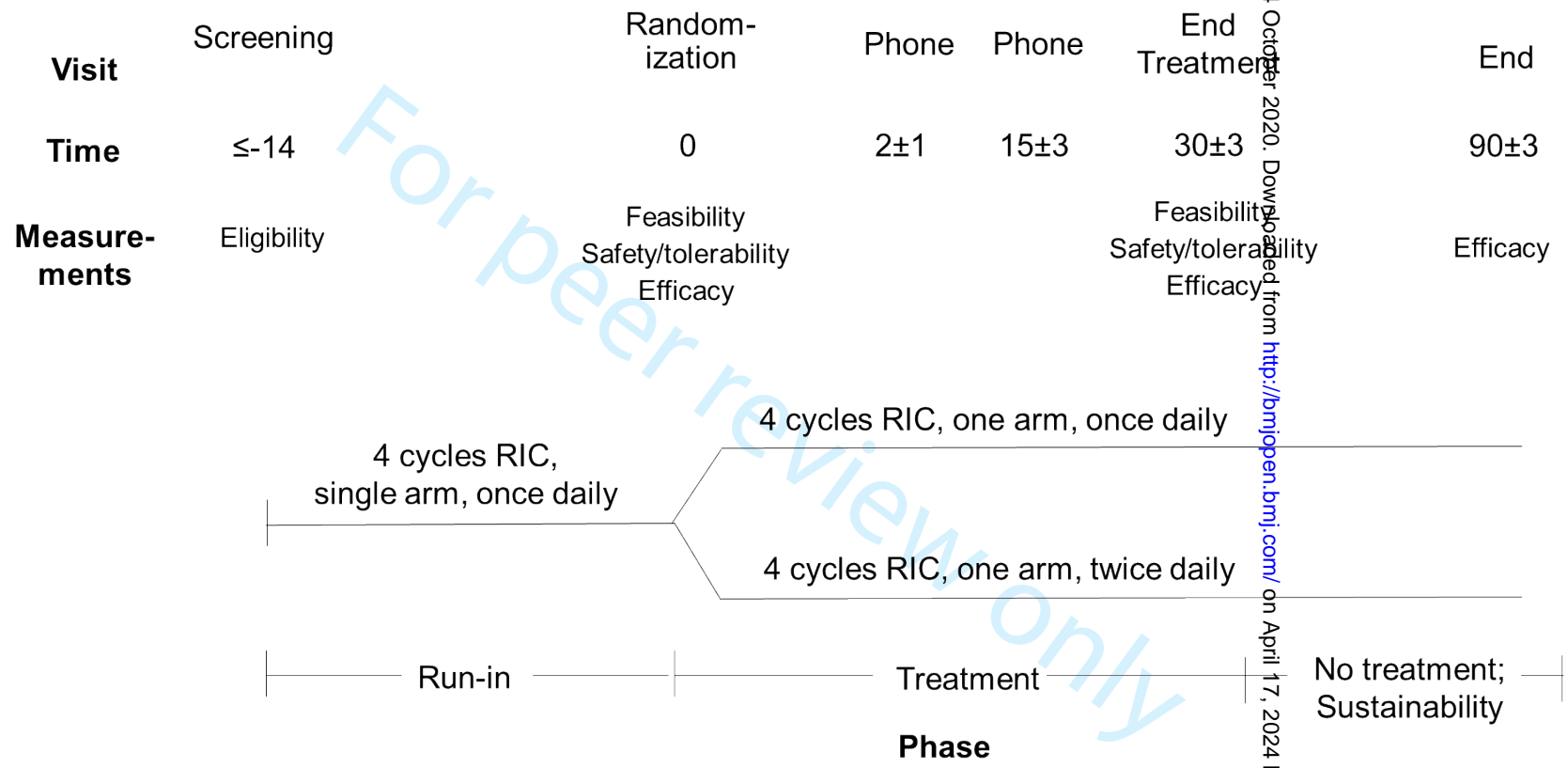


Figure 1. Trial design for the TRIC-VCI study.

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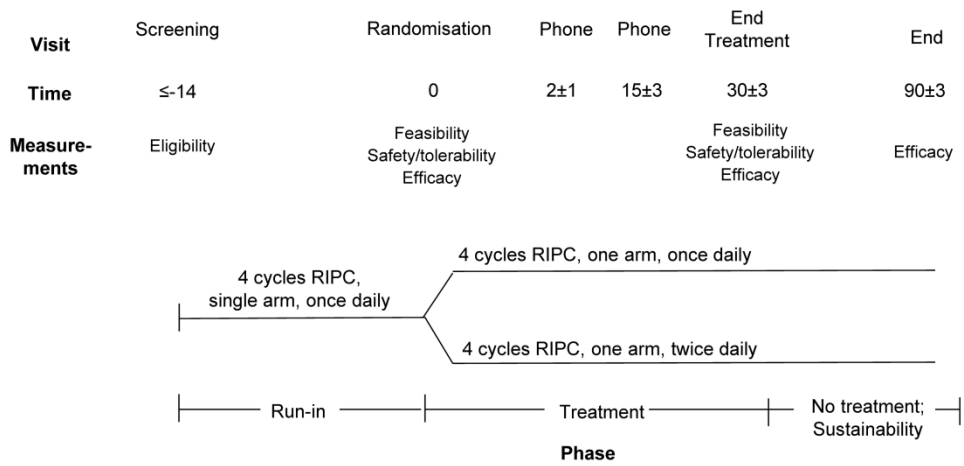


Figure 1. Trial design for the TRIC-VCI study.

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: <ol style="list-style-type: none"> 1. Patient declares unwillingness to proceed with the intervention, OR 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 measure 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.psm-d-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 encephalomalacia 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: <ol style="list-style-type: none"> 1. Mean change in total MoCA scores. 2. Proportion with decline in total MoCA ≥ 2 points. 3. Mean change in MoCA visuospatial/executive subscore. 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: <ol style="list-style-type: none"> 1. Homocysteine 2. Circulating nitrite 3. Interleukin-10 4. Matrix metalloproteinase 2 and 9 5. TNF-alpha 6. Interferon gamma 7. MicroRNA-144 8. SDF-1-alpha 9. Heat shock protein 27

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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 Score⁵⁰.
- Cognitive performance, using the MoCA.
- Informant reports of cognitive decline and functional status using BADLS, AD8, and IQCODE short form⁵¹ 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 $\geq 80\%$ 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 $\geq 80\%$ 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 $\geq 80\%$ 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
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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 Radiology⁵⁸, 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	<i>b</i> =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.

Peer review only

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.

Ethics ID: REB19-0861

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

PI: Dr. Eric E. Smith

Version 4.0

Date: January 7, 2020 peer review only - <http://bmjopen.bmj.com/site/about/guidelines.xhtml> Page 1 of 12

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.

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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).

Ethics ID: REB19-0861

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- 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

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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 do not 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

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PI: Dr. Eric E. Smith

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- 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.

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Potential Interactions with Other Medications: You can continue to take all your 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.

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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.

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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.

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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.**

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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 (! ! " # # # "\$\$)
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Investigator Name	Signature	Date (! ! " # # # "\$\$)
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Witness' Name	Signature	Date (! ! " # # # "\$\$)
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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.

Ethics ID: REB19-0861

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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.

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CRU #044 TRIC VCI

Plate #001

Screening

Subject ID:

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Centre

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Subject ID

Date:

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SCREENING (page 1 of 6)

Has the research candidate and their study partner given informed consent and signed the consent forms?	<input type="checkbox"/> Yes	<input type="checkbox"/> No
---	------------------------------	-----------------------------

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





CRU #044 TRIC VCI

Plate #002

Screening

Subject ID:

Centre Subject ID

Date:

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SCREENING (page 2 of 6)

EXCLUSION CRITERIA: All responses must be NO to qualify:

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

Signature of investigator confirms the Inclusion/Exclusion Criteria : _____

e-signature
iDataFax use only

:

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PI's printed first and last name: _____





CRU #044 TRIC VCI

Plate #003

Screening

Subject ID:

Centre

Subject ID

Date:

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SCREENING (page 3 of 6)

DEMOGRAPHICS

1. Age:	<input type="text"/> <input type="text"/>												
2. Sex:	<input type="checkbox"/> Male <input type="checkbox"/> Female												
3. Mother tongue (first language learned):	<input type="checkbox"/> English <input type="checkbox"/> French <input type="checkbox"/> Other: _____												
4. Marital Status:	<input type="checkbox"/> Single <input type="checkbox"/> Separated <input type="checkbox"/> Married <input type="checkbox"/> Divorced <input type="checkbox"/> Common-law partnership <input type="checkbox"/> Widowed												
5. Current living circumstance:	<input type="checkbox"/> House or apartment/condominium that you own <input type="checkbox"/> Apartment/condominium or house that you rent <input type="checkbox"/> Retirement home (autonomous living) <input type="checkbox"/> Residence for semi-autonomous individuals <input type="checkbox"/> Nursing home or long-term care (assisted living) <input type="checkbox"/> Other, please specify: _____												
6. What is the highest grade or level of school completed or highest degree obtained:	<table border="0"> <tr> <td><input type="checkbox"/> Never attended school</td> <td><input type="checkbox"/> Technical school or community college</td> </tr> <tr> <td><input type="checkbox"/> Some primary/grade school</td> <td><input type="checkbox"/> CEGEP</td> </tr> <tr> <td><input type="checkbox"/> Completed primary/grade school</td> <td><input type="checkbox"/> Undergraduate degree at university (e.g., B.A, B.SC, B.Eng., LL.B., B.Ed., etc)</td> </tr> <tr> <td><input type="checkbox"/> Some high school</td> <td></td> </tr> <tr> <td><input type="checkbox"/> Completed high school</td> <td><input type="checkbox"/> Some graduate (post-undergraduate) school</td> </tr> <tr> <td><input type="checkbox"/> Apprenticeship</td> <td><input type="checkbox"/> Graduate degree at university</td> </tr> </table>	<input type="checkbox"/> Never attended school	<input type="checkbox"/> Technical school or community college	<input type="checkbox"/> Some primary/grade school	<input type="checkbox"/> CEGEP	<input type="checkbox"/> Completed primary/grade school	<input type="checkbox"/> Undergraduate degree at university (e.g., B.A, B.SC, B.Eng., LL.B., B.Ed., etc)	<input type="checkbox"/> Some high school		<input type="checkbox"/> Completed high school	<input type="checkbox"/> Some graduate (post-undergraduate) school	<input type="checkbox"/> Apprenticeship	<input type="checkbox"/> Graduate degree at university
<input type="checkbox"/> Never attended school	<input type="checkbox"/> Technical school or community college												
<input type="checkbox"/> Some primary/grade school	<input type="checkbox"/> CEGEP												
<input type="checkbox"/> Completed primary/grade school	<input type="checkbox"/> Undergraduate degree at university (e.g., B.A, B.SC, B.Eng., LL.B., B.Ed., etc)												
<input type="checkbox"/> Some high school													
<input type="checkbox"/> Completed high school	<input type="checkbox"/> Some graduate (post-undergraduate) school												
<input type="checkbox"/> Apprenticeship	<input type="checkbox"/> Graduate degree at university												





CRU #044 TRIC VCI

Plate #004

Screening

Subject ID:

Centre

Subject ID

Date:

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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

For peer review only





CRU #044 TRIC VCI

Plate #005

Screening

Subject ID:

Centre Subject ID

Date:

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SCREENING (page 5 of 6)

MEDICAL HISTORY	
1. History of prior transient ischemic attack:	<input type="checkbox"/> Yes <input type="checkbox"/> No
If yes, then complete 1.a. and 1.b.	
1.a. Is there a history of more than one prior transient ischemic attack?	<input type="checkbox"/> Yes <input type="checkbox"/> No
1.b. What was the month and year of the most recent prior transient attack?	<input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/>
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2. History of prior stroke:	<input type="checkbox"/> Yes <input type="checkbox"/> No
If yes, then complete 2.a and 2.b.	
2.a. Is there a history of more than one prior stroke?	<input type="checkbox"/> Yes <input type="checkbox"/> No
2.b. What was the month and year of the most recent prior stroke?	<input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/>
	y y y y m m
3. History of carotid stenosis:	<input type="checkbox"/> Yes <input type="checkbox"/> No
4. History of prior carotid revascularization:	<input type="checkbox"/> Yes <input type="checkbox"/> No
4.a. Side of carotid revascularization:	<input type="checkbox"/> R <input type="checkbox"/> L <input type="checkbox"/> Both
5. History of hypertension or use of antihypertensive medications to control blood pressure:	<input type="checkbox"/> Yes <input type="checkbox"/> No
6. History of diabetes mellitus:	<input type="checkbox"/> Yes <input type="checkbox"/> No
7. History of dyslipidemia or use of antilipid medications:	<input type="checkbox"/> Yes <input type="checkbox"/> No
8. History of myocardial infarction:	<input type="checkbox"/> Yes <input type="checkbox"/> No
9. History of angina:	<input type="checkbox"/> Yes <input type="checkbox"/> No
<input type="checkbox"/> W R B I D W L D O E L U O O D W L R Q	<input type="checkbox"/> Yes <input type="checkbox"/> No
11. History of heart failure:	<input type="checkbox"/> Yes <input type="checkbox"/> No



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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:	<input type="checkbox"/> Yes <input type="checkbox"/> No
13. History of prior deep venous thrombosis:	<input type="checkbox"/> Yes <input type="checkbox"/> No
14. History of prior cancer:	<input type="checkbox"/> Yes <input type="checkbox"/> No
15. History of any other central nervous system diseases (list):	
<hr/>	
<hr/>	





CRU #044 TRIC VCI

Plate #007

Screening Randomization
 Follow Up End

Subject ID:

<i>Centre</i>		<i>Subject ID</i>	

Date:

<i>yyyy</i>				<i>mm</i>		<i>dd</i>	

MEDICATIONS

1. Is the patient taking an antiplatelet drug?	<input type="checkbox"/> Yes <input type="checkbox"/> No
If yes, please answer 1.a. below:	
1.a. Antiplatelet drug class(es)—select all that apply:	
<input type="checkbox"/> Acetylsalicylic acid (e.g. Aspirin)	<input type="checkbox"/> Persantine
<input type="checkbox"/> Clopidogrel (Plavix)	<input type="checkbox"/> Ticagrelor (Brilinta)
<input type="checkbox"/> Aggrenox	<input type="checkbox"/> Prasugrel (Effient)
2. Is the patient taking an anticoagulant drug?	<input type="checkbox"/> Yes <input type="checkbox"/> 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?	<input type="checkbox"/> Yes <input type="checkbox"/> No

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

Signature: _____	Date: <table border="1" style="display: inline-table; vertical-align: middle;"> <tr> <td style="width: 30px; height: 30px;"></td> <td style="width: 30px; height: 30px;"></td> <td style="width: 30px; height: 30px;"></td> <td style="width: 30px; height: 30px;"></td> <td style="width: 30px; height: 30px;"></td> <td style="width: 30px; height: 30px;"></td> <td style="width: 30px; height: 30px;"></td> <td style="width: 30px; height: 30px;"></td> </tr> <tr> <td colspan="4" style="text-align: center;"><i>yyyy</i></td> <td colspan="2" style="text-align: center;"><i>mm</i></td> <td colspan="2" style="text-align: center;"><i>dd</i></td> </tr> </table>									<i>yyyy</i>				<i>mm</i>		<i>dd</i>	
<i>yyyy</i>				<i>mm</i>		<i>dd</i>											





CRU #044 TRIC VCI

Plate #008

Screening Randomization
 Follow Up

Subject ID:
 Centre Subject ID

Date:
 y y y y m m d d

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	<input type="checkbox"/> Yes	<input type="checkbox"/> No	<input type="checkbox"/> Yes	<input type="checkbox"/> No
Ulnar pulse palpable	<input type="checkbox"/> Yes	<input type="checkbox"/> No	<input type="checkbox"/> Yes	<input type="checkbox"/> No
Brachial pulse palpable	<input type="checkbox"/> Yes	<input type="checkbox"/> No	<input type="checkbox"/> Yes	<input type="checkbox"/> No
Local edema	<input type="checkbox"/> Yes	<input type="checkbox"/> No	<input type="checkbox"/> Yes	<input type="checkbox"/> No
Skin breakdown	<input type="checkbox"/> Yes	<input type="checkbox"/> No	<input type="checkbox"/> Yes	<input type="checkbox"/> No
Rash	<input type="checkbox"/> Yes	<input type="checkbox"/> No	<input type="checkbox"/> Yes	<input type="checkbox"/> No
Petechiae	<input type="checkbox"/> Yes	<input type="checkbox"/> No	<input type="checkbox"/> Yes	<input type="checkbox"/> No
Upper arm tenderness	<input type="checkbox"/> Yes	<input type="checkbox"/> No	<input type="checkbox"/> Yes	<input type="checkbox"/> No
Lower arm tenderness	<input type="checkbox"/> Yes	<input type="checkbox"/> No	<input type="checkbox"/> Yes	<input type="checkbox"/> No

3. Arm examination comments:

4. Examiner blinded to treatment arm: Yes No

Signature: _____ Date:
 y y y y m m d d





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	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>	0 - Alert 1 - Not alert, but arousable with minimal stimulation 2 - Not alert, requires repeated stimulation to attend 3 - Coma
1b. LOC Questions <i>Ask patient the month and their age</i>	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>	0 - Answers both correctly 1 - Answers one correctly 2 - Both incorrect
1c. LOC Commands <i>Ask patient to open/close eyes and form/release fist</i>	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>	0 - Obeys both correctly 1 - Obeys one correctly 2 - Both incorrect
2. Best Gaze <i>Only horizontal eye movement</i>	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>	0 - Normal 1 - Partial gaze palsy 2 - Forced gaze palsy
3. Visual Field Testing	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>	0 - No visual field loss 1 - Partial hemianopia 2 - Complete hemianopia 3 - Bilateral hemianopia (blind, incl. Cortical blindness)
4. Facial Palsy <i>Ask patient to show teeth or raise eyebrows and close eyes tightly</i>	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>	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:

y y y y

m m

d d

NIH STROKE SCALE (page 2 of 3)

	L	R	
5. Motor Function Arm	<input type="checkbox"/>	<input type="checkbox"/>	0 - Normal (extends arm 90° or 45° for 10 sec without drift)
	<input type="checkbox"/>	<input type="checkbox"/>	1 - Drift
	<input type="checkbox"/>	<input type="checkbox"/>	2 - Some effort against gravity
	<input type="checkbox"/>	<input type="checkbox"/>	3 - No effort against gravity
	<input type="checkbox"/>	<input type="checkbox"/>	4 - No movement
	<input type="checkbox"/>	<input type="checkbox"/>	9 - Untestable (Joint fused/limb amputated) (<i>do not add score</i>)
	L	R	
6. Motor Function Leg	<input type="checkbox"/>	<input type="checkbox"/>	0 - Normal (holds leg in 30° position for 5 sec without drift)
	<input type="checkbox"/>	<input type="checkbox"/>	1 - Drift
	<input type="checkbox"/>	<input type="checkbox"/>	2 - Some effort against gravity
	<input type="checkbox"/>	<input type="checkbox"/>	3 - No effort against gravity
	<input type="checkbox"/>	<input type="checkbox"/>	4 - No movement
	<input type="checkbox"/>	<input type="checkbox"/>	9 - Untestable (Joint fused/limb amputated) (<i>do not add score</i>)
7. Limb ataxia	<input type="checkbox"/>		0 - No ataxia
	<input type="checkbox"/>		1 - Present in one limb
	<input type="checkbox"/>		2 - Present in two limbs
8. Sensory <i>Use pinprick to test arms, legs, trunk and face, compare side to side</i>	<input type="checkbox"/>		0 - Normal
	<input type="checkbox"/>		1 - Mild to moderate decrease in sensation
	<input type="checkbox"/>		2 - Severe to total sensory loss
9. Best Language <i>Ask patient to describe picture, name items</i>	<input type="checkbox"/>		0 - No aphasia
	<input type="checkbox"/>		1 - Mild to moderate aphasia
	<input type="checkbox"/>		2 - Severe aphasia
	<input type="checkbox"/>		3 - Mute



CRU #044 TRIC VCI

Plate #011

Screening Randomization
 Follow Up End

Subject ID:
Centre *Subject ID*

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

NIH STROKE SCALE *(page 3 of 3)*

<p>10. Dysarthria <i>Ask patient to read several words</i></p>	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>	<p>0 - No aphasia</p> <p>1 - Mild to moderate slurring of words</p> <p>2 - Near unintelligible or unable to speak</p> <p>9 - Intubated or other physical barrier (<i>do not add score</i>)</p>
--	--	--

<p>11. Extinction and Inattention <i>Use visual double stimulation or sensory double stimulation</i></p>	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>	<p>0 - Normal</p> <p>1 - Inattention or extinction to bilateral simultaneous stimulation in one of the sensory modalities</p> <p>2 - Hemi-inattention, severe or to more than one modality</p>
--	--	--

Auto-Calculated Total Score Only:
[range 0-42]

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





CRU #044 TRIC VCI

Plate #012

Screening

Subject ID:
Centre Subject ID

Date:
y y y y m m d d

HACHINSKI ISCHEMIC SCORE

Characteristic	YES	NO
Abrupt onset	<input type="checkbox"/> ₂	<input type="checkbox"/> ₀
Stepwise deterioration	<input type="checkbox"/> ₁	<input type="checkbox"/> ₀
Fluctuating course	<input type="checkbox"/> ₂	<input type="checkbox"/> ₀
Nocturnal confusion	<input type="checkbox"/> ₁	<input type="checkbox"/> ₀
Preservation of personality	<input type="checkbox"/> ₁	<input type="checkbox"/> ₀
Depression	<input type="checkbox"/> ₁	<input type="checkbox"/> ₀
Somatic complaints	<input type="checkbox"/> ₁	<input type="checkbox"/> ₀
Emotional lability	<input type="checkbox"/> ₁	<input type="checkbox"/> ₀
History of hypertension	<input type="checkbox"/> ₁	<input type="checkbox"/> ₀
History of stroke	<input type="checkbox"/> ₂	<input type="checkbox"/> ₀
Associated atherosclerosis	<input type="checkbox"/> ₁	<input type="checkbox"/> ₀
Focal neurological symptoms	<input type="checkbox"/> ₂	<input type="checkbox"/> ₀
Focal neurological signs	<input type="checkbox"/> ₂	<input type="checkbox"/> ₀

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

Signature: _____ Date:
y y y y m m d d





CRU #044 TRIC VCI

Plate #013

Screening Randomization

Follow Up End

Subject ID:

Centre

Subject ID

Date:

y y y y

m m

d d

MONTREAL COGNITIVE ASSESSMENT (page 1 of 2)

<p>VISUOSPATIAL / EXECUTIVE</p> <p>Copy cube</p> <p><input type="checkbox"/> <input type="checkbox"/></p>	<p>Draw CLOCK (Ten past eleven) (3 points)</p> <p><input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/></p> <p>Contour Numbers Hands</p>	<p>POINTS</p> <p><input type="text"/> /5</p>																		
<p>NAMING</p> <p><input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/></p>		<p><input type="text"/> /3</p>																		
<p>MEMORY</p> <p>Read list of words, subject must repeat them. Do 2 trials. Do a recall after 5 minutes.</p>	<table border="1"> <tr> <td></td> <td>FACE</td> <td>VELVET</td> <td>CHURCH</td> <td>DAISY</td> <td>RED</td> </tr> <tr> <td>1st trial</td> <td><input type="checkbox"/></td> <td><input type="checkbox"/></td> <td><input type="checkbox"/></td> <td><input type="checkbox"/></td> <td><input type="checkbox"/></td> </tr> <tr> <td>2nd trial</td> <td><input type="checkbox"/></td> <td><input type="checkbox"/></td> <td><input type="checkbox"/></td> <td><input type="checkbox"/></td> <td><input type="checkbox"/></td> </tr> </table>		FACE	VELVET	CHURCH	DAISY	RED	1st trial	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	2nd trial	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<p>No Points</p>
	FACE	VELVET	CHURCH	DAISY	RED															
1st trial	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>															
2nd trial	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>															
<p>ATTENTION</p> <p>Read list of digits (1 digit/sec).</p> <p>Subject has to repeat them in the forward order <input type="checkbox"/> 2 1 8 5 4</p> <p>Subject has to repeat them in the backward order <input type="checkbox"/> 7 4 2</p>	<p><input type="text"/> /2</p>																			
<p>Read list of letters. The subject must tap with his hand at each letter A. No points if ≥ 2 errors</p> <p><input type="checkbox"/> 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</p>		<p><input type="text"/> /1</p>																		
<p>Serial 7 subtraction starting at 100 <input type="checkbox"/> 93 <input type="checkbox"/> 86 <input type="checkbox"/> 79 <input type="checkbox"/> 72 <input type="checkbox"/> 65</p> <p>4 or 5 correct subtractions: 3 pts, 2 or 3 correct: 2 pts, 1 correct: 1 pt, 0 correct: 0 pt</p>		<p><input type="text"/> /3</p>																		





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

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Centre

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Subject ID

Date:

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





CRU #044 TRIC VCI

Plate #016

 Screening Randomization
 Follow Up End

Subject ID:

Centre

Subject ID

Date:

y y y y

m m

d d

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

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



CRU #044 TRIC VCI

Plate #017

Screening Randomization

Follow Up End

Subject ID:

Centre

Subject ID

Date:

y y y y

m m

d d

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

8. BATH/SHOWER	<input type="checkbox"/>	a) Bathes regularly and independently
	<input type="checkbox"/>	b) Needs bath to be drawn/shower turned on but washes independently
	<input type="checkbox"/>	c) Needs supervision and prompting to wash
	<input type="checkbox"/>	d) Totally dependent, needs full assistance
	<input type="checkbox"/>	e) Not applicable
9. TOILET/COMMODE	<input type="checkbox"/>	a) Uses toilet appropriately when required
	<input type="checkbox"/>	b) Needs to be taken to the toilet and given assistance
	<input type="checkbox"/>	c) Incontinent of urine or faeces
	<input type="checkbox"/>	d) Incontinent of urine and faeces
	<input type="checkbox"/>	e) Not applicable
10. TRANSFERS	<input type="checkbox"/>	a) Can get in/out of chair unaided
	<input type="checkbox"/>	b) Can get into a chair but needs help to get out
	<input type="checkbox"/>	c) Needs help getting in and out of a chair
	<input type="checkbox"/>	d) Totally dependent on being put into and lifted from chair
	<input type="checkbox"/>	e) Not applicable
11. MOBILITY	<input type="checkbox"/>	a) Walks independently
	<input type="checkbox"/>	b) Walks with assistance i.e. furniture, arm for support
	<input type="checkbox"/>	c) Uses aids to mobilise i.e. frame, sticks etc.
	<input type="checkbox"/>	d) Unable to walk
	<input type="checkbox"/>	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	<input type="checkbox"/>	a) Fully orientated to time/day/date etc.
	<input type="checkbox"/>	b) Unaware of time/day etc. but seems unconcerned
	<input type="checkbox"/>	c) Repeatedly asks the time/day/date
	<input type="checkbox"/>	d) Mixes up night and day
	<input type="checkbox"/>	e) Not applicable
13. ORIENTATION – SPACE	<input type="checkbox"/>	a) Fully orientated to surroundings
	<input type="checkbox"/>	b) Orientated to familiar surroundings only
	<input type="checkbox"/>	c) Gets lost in home, needs reminding where bathroom is, etc.
	<input type="checkbox"/>	d) Does not recognise home as own and attempts to leave
	<input type="checkbox"/>	e) Not applicable
14. COMMUNICATION	<input type="checkbox"/>	a) Able to hold appropriate conversation
	<input type="checkbox"/>	b) Shows understanding and attempts to respond verbally with gestures
	<input type="checkbox"/>	c) Can make self-understood but difficulty understanding others
	<input type="checkbox"/>	d) Does not respond to, or communicate with others
	<input type="checkbox"/>	e) Not applicable
15. TELEPHONE	<input type="checkbox"/>	a) Uses telephone appropriately, including obtaining correct number
	<input type="checkbox"/>	b) Uses telephone if number given verbally/visually or predialed
	<input type="checkbox"/>	c) Answers telephone but does not make calls
	<input type="checkbox"/>	d) Unable/unwilling to use telephone at all
	<input type="checkbox"/>	e) Not applicable



CRU #044 TRIC VCI

Plate #019

- Screening
- Randomization
- Follow Up
- End

Subject ID:

<i>Centre</i>	<i>Subject ID</i>		

Date:

<i>y y y y</i>				<i>m m</i>		<i>d d</i>

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

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





CRU #044 TRIC VCI

Plate #020

 Screening Randomization
 Follow Up End

Subject ID:

Centre

Subject ID

Date:

y y y y

m m

d d

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

19. GAMES/HOBBIES	<input type="checkbox"/>	a) Participates in pastimes/activities to previous standard
	<input type="checkbox"/>	b) Participates but needs instruction/supervision
	<input type="checkbox"/>	c) Reluctant to join in, very slow needs coaxing
	<input type="checkbox"/>	d) No longer able or willing to join in
	<input type="checkbox"/>	e) Not applicable
20. TRANSPORT	<input type="checkbox"/>	a) Able to drive, cycle or use public transport independently
	<input type="checkbox"/>	b) Unable to drive but uses public transport or bike etc.
	<input type="checkbox"/>	c) Unable to use public transport alone
	<input type="checkbox"/>	d) Unable/unwilling to use transport even when accompanied
	<input type="checkbox"/>	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)	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
2. Less interest in hobbies/activities	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
3. Repeats the same things over and over (questions, stories, or statements)	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
4. Trouble learning how to use a tool, appliance, or gadget (e.g., VCR, computer, microwave, remote control)	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
5. Forgets correct month or year	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
6. Trouble handling complicated financial affairs (e.g., balancing checkbook, income taxes, paying bills)	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
7. Trouble remembering appointments	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
8. Daily problems with thinking and/or memory	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Total Score [0-8]			<input type="text"/>





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	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
2. Remembering things that have happened recently	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
3. Recalling conversations a few days later	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
4. Remembering his/her address and telephone number	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
5. Remembering what day and month it is	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
6. Remembering where things are usually kept	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
7. Remembering where to find things which have been put in a different place from usual	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
8. Knowing how to work familiar machines around the house	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
9. Learning to use a new gadget or machine around the house	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
10. Learning new things in general	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
11. Following a story in a book or on TV	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
12. Making decisions on everyday matters	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>



CRU #044 TRIC VCI

Plate #023

Screening

Subject ID:

Centre

Subject ID

Date:

yyyy

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INFORMANT IQCODE (page 2 of 2)

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



1  Randomization End
 2
 3 CRU #044 TRIC VCI Plate #024 Follow Up
 4
 5 Subject ID: Date:
 6 Centre Subject ID y y y y m m d d
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8 **INFORMANT MBI TRACKING TOOL** (page 1 of 3)

9
10
11 Please score each item for its presence over the **last 2 weeks** (continuously or on and off). If present, items
12 should reflect a **change** from the longstanding pattern of behavior. Otherwise, check "No".

13
14 Please rate severity: **1 = Mild** (noticeable, but of minor significance); **2 = Moderate** (significant, but not
15 dramatic); **3 = Severe** (very marked or prominent, or dramatic change). If more than 1 item in a question, rate
16 the most severe.
17

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



CRU #044 TRIC VCI

Plate #025

Randomization End

Follow Up

Subject ID:

Centre

Subject ID

Date:

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INFORMANT MBI TRACKING TOOL (page 2 of 3)

	YES	NO	SEVERITY
<i>This domain describes the ability to delay gratification and control behavior, impulses, oral intake and/or changes in reward</i>			
Agitation, aggression, irritability, or being temperamental.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/> ₁ <input type="checkbox"/> ₂ <input type="checkbox"/> ₃
Being unreasonably or uncharacteristically argumentative.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/> ₁ <input type="checkbox"/> ₂ <input type="checkbox"/> ₃
Impulsivity. Seeming to act without considering things.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/> ₁ <input type="checkbox"/> ₂ <input type="checkbox"/> 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.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/> ₁ <input type="checkbox"/> ₂ <input type="checkbox"/> ₃
Frustration or impatience. Having troubles coping with delays, or waiting for events or for one's turn?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/> ₁ <input type="checkbox"/> ₂ <input type="checkbox"/> ₃
Recklessness or lack of judgement when driving (e.g. speeding, erratic swerving, abrupt lane changes, etc.).	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/> ₁ <input type="checkbox"/> ₂ <input type="checkbox"/> ₃
Stubbornness or rigidity, i.e., uncharacteristically insistent on having one's own way, or being unwilling/unable to see/hear other views.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/> ₁ <input type="checkbox"/> ₂ <input type="checkbox"/> 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).	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/> ₁ <input type="checkbox"/> ₂ <input type="checkbox"/> ₃
Not finding food tasteful or enjoyable. Eating less.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/> ₁ <input type="checkbox"/> ₂ <input type="checkbox"/> ₃
Hoarding objects.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/> ₁ <input type="checkbox"/> ₂ <input type="checkbox"/> ₃
Simple repetitive behaviors or compulsions.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/> ₁ <input type="checkbox"/> ₂ <input type="checkbox"/> ₃
Trouble regulating smoking, alcohol, drug intake, gambling, or shoplifting.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/> ₁ <input type="checkbox"/> ₂ <input type="checkbox"/> ₃
<i>This domain describes following societal norms and having social graces, tact, and empathy</i>			
Unconcerned about how one's words or actions affect others. Insensitivity to others' feelings.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/> ₁ <input type="checkbox"/> ₂ <input type="checkbox"/> ₃
Talking openly about very personal or private matters not usually discussed in public.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/> ₁ <input type="checkbox"/> ₂ <input type="checkbox"/> ₃
Saying rude or crude things or making lewd sexual remarks.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/> ₁ <input type="checkbox"/> ₂ <input type="checkbox"/> ₃
Lacking the social judgement about what to say or how to behave in public or private.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/> ₁ <input type="checkbox"/> ₂ <input type="checkbox"/> ₃
Talking to strangers as if familiar, or intruding on their activities.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/> ₁ <input type="checkbox"/> ₂ <input type="checkbox"/> 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
<i>This domain describes strongly held beliefs and sensory experiences</i>			
Having beliefs that one is in danger, or that others are planning harm or to steal one's belongings.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/> 1 <input type="checkbox"/> 2 <input type="checkbox"/> 3
Suspiciousness about the intentions or motives of other people.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/> 1 <input type="checkbox"/> 2 <input type="checkbox"/> 3
Unrealistic beliefs about one's power, wealth or skills.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/> 1 <input type="checkbox"/> 2 <input type="checkbox"/> 3
Hearing voices or talking to imaginary people or "spirits".	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/> 1 <input type="checkbox"/> 2 <input type="checkbox"/> 3
Seeing things (e.g. people, animals or insects) that are not there, i.e., that are imaginary to others?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/> 1 <input type="checkbox"/> 2 <input type="checkbox"/> 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	----	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/>	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> 0 1 2 3 4 5 <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> 6 7 8 9 10
2	----	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/>	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> 0 1 2 3 4 5 <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> 6 7 8 9 10
3	----	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/>	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> 0 1 2 3 4 5 <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> 6 7 8 9 10
4	----	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/>	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> 0 1 2 3 4 5 <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> 6 7 8 9 10
5	----	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/>	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> 0 1 2 3 4 5 <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> 6 7 8 9 10
6	----	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/>	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> 0 1 2 3 4 5 <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> 6 7 8 9 10
7	----	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/>	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> 0 1 2 3 4 5 <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> 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	----	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/>	<input type="checkbox"/> 0 <input type="checkbox"/> 1 <input type="checkbox"/> 2 <input type="checkbox"/> 3 <input type="checkbox"/> 4 <input type="checkbox"/> 5 <input type="checkbox"/> 6 <input type="checkbox"/> 7 <input type="checkbox"/> 8 <input type="checkbox"/> 9 <input type="checkbox"/> 10
2	----	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/>	<input type="checkbox"/> 0 <input type="checkbox"/> 1 <input type="checkbox"/> 2 <input type="checkbox"/> 3 <input type="checkbox"/> 4 <input type="checkbox"/> 5 <input type="checkbox"/> 6 <input type="checkbox"/> 7 <input type="checkbox"/> 8 <input type="checkbox"/> 9 <input type="checkbox"/> 10
3	----	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/>	<input type="checkbox"/> 0 <input type="checkbox"/> 1 <input type="checkbox"/> 2 <input type="checkbox"/> 3 <input type="checkbox"/> 4 <input type="checkbox"/> 5 <input type="checkbox"/> 6 <input type="checkbox"/> 7 <input type="checkbox"/> 8 <input type="checkbox"/> 9 <input type="checkbox"/> 10
4	----	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/>	<input type="checkbox"/> 0 <input type="checkbox"/> 1 <input type="checkbox"/> 2 <input type="checkbox"/> 3 <input type="checkbox"/> 4 <input type="checkbox"/> 5 <input type="checkbox"/> 6 <input type="checkbox"/> 7 <input type="checkbox"/> 8 <input type="checkbox"/> 9 <input type="checkbox"/> 10
5	----	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/>	<input type="checkbox"/> 0 <input type="checkbox"/> 1 <input type="checkbox"/> 2 <input type="checkbox"/> 3 <input type="checkbox"/> 4 <input type="checkbox"/> 5 <input type="checkbox"/> 6 <input type="checkbox"/> 7 <input type="checkbox"/> 8 <input type="checkbox"/> 9 <input type="checkbox"/> 10
6	----	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/>	<input type="checkbox"/> 0 <input type="checkbox"/> 1 <input type="checkbox"/> 2 <input type="checkbox"/> 3 <input type="checkbox"/> 4 <input type="checkbox"/> 5 <input type="checkbox"/> 6 <input type="checkbox"/> 7 <input type="checkbox"/> 8 <input type="checkbox"/> 9 <input type="checkbox"/> 10
7	----	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/>	<input type="checkbox"/> 0 <input type="checkbox"/> 1 <input type="checkbox"/> 2 <input type="checkbox"/> 3 <input type="checkbox"/> 4 <input type="checkbox"/> 5 <input type="checkbox"/> 6 <input type="checkbox"/> 7 <input type="checkbox"/> 8 <input type="checkbox"/> 9 <input type="checkbox"/> 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	----	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/>	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> 0 1 2 3 4 5 <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> 6 7 8 9 10
2	----	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/>	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> 0 1 2 3 4 5 <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> 6 7 8 9 10
3	----	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/>	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> 0 1 2 3 4 5 <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> 6 7 8 9 10
4	----	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/>	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> 0 1 2 3 4 5 <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> 6 7 8 9 10
5	----	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/>	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> 0 1 2 3 4 5 <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> 6 7 8 9 10
6	----	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/>	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> 0 1 2 3 4 5 <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> 6 7 8 9 10
7	----	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/>	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> 0 1 2 3 4 5 <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> 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	----	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/>	<input type="checkbox"/> 0 <input type="checkbox"/> 1 <input type="checkbox"/> 2 <input type="checkbox"/> 3 <input type="checkbox"/> 4 <input type="checkbox"/> 5 <input type="checkbox"/> 6 <input type="checkbox"/> 7 <input type="checkbox"/> 8 <input type="checkbox"/> 9 <input type="checkbox"/> 10
2	----	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/>	<input type="checkbox"/> 0 <input type="checkbox"/> 1 <input type="checkbox"/> 2 <input type="checkbox"/> 3 <input type="checkbox"/> 4 <input type="checkbox"/> 5 <input type="checkbox"/> 6 <input type="checkbox"/> 7 <input type="checkbox"/> 8 <input type="checkbox"/> 9 <input type="checkbox"/> 10
3	----	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/>	<input type="checkbox"/> 0 <input type="checkbox"/> 1 <input type="checkbox"/> 2 <input type="checkbox"/> 3 <input type="checkbox"/> 4 <input type="checkbox"/> 5 <input type="checkbox"/> 6 <input type="checkbox"/> 7 <input type="checkbox"/> 8 <input type="checkbox"/> 9 <input type="checkbox"/> 10
4	----	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/>	<input type="checkbox"/> 0 <input type="checkbox"/> 1 <input type="checkbox"/> 2 <input type="checkbox"/> 3 <input type="checkbox"/> 4 <input type="checkbox"/> 5 <input type="checkbox"/> 6 <input type="checkbox"/> 7 <input type="checkbox"/> 8 <input type="checkbox"/> 9 <input type="checkbox"/> 10
5	----	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/>	<input type="checkbox"/> 0 <input type="checkbox"/> 1 <input type="checkbox"/> 2 <input type="checkbox"/> 3 <input type="checkbox"/> 4 <input type="checkbox"/> 5 <input type="checkbox"/> 6 <input type="checkbox"/> 7 <input type="checkbox"/> 8 <input type="checkbox"/> 9 <input type="checkbox"/> 10
6	----	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/>	<input type="checkbox"/> 0 <input type="checkbox"/> 1 <input type="checkbox"/> 2 <input type="checkbox"/> 3 <input type="checkbox"/> 4 <input type="checkbox"/> 5 <input type="checkbox"/> 6 <input type="checkbox"/> 7 <input type="checkbox"/> 8 <input type="checkbox"/> 9 <input type="checkbox"/> 10
7	----	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/>	<input type="checkbox"/> 0 <input type="checkbox"/> 1 <input type="checkbox"/> 2 <input type="checkbox"/> 3 <input type="checkbox"/> 4 <input type="checkbox"/> 5 <input type="checkbox"/> 6 <input type="checkbox"/> 7 <input type="checkbox"/> 8 <input type="checkbox"/> 9 <input type="checkbox"/> 10





CRU #044 TRIC VCI

Plate #031

Follow Up

Subject ID:

<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>
Centre		Subject ID		

Date:

<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>
yyyy				mm		dd

PATIENT DIARY - ONCE DAILY - WEEK 2

Date that the week started on:

<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>
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	----	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="text"/> <input type="text"/>	<input type="checkbox"/> 0 <input type="checkbox"/> 1 <input type="checkbox"/> 2 <input type="checkbox"/> 3 <input type="checkbox"/> 4 <input type="checkbox"/> 5 <input type="checkbox"/> 6 <input type="checkbox"/> 7 <input type="checkbox"/> 8 <input type="checkbox"/> 9 <input type="checkbox"/> 10
2	----	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="text"/> <input type="text"/>	<input type="checkbox"/> 0 <input type="checkbox"/> 1 <input type="checkbox"/> 2 <input type="checkbox"/> 3 <input type="checkbox"/> 4 <input type="checkbox"/> 5 <input type="checkbox"/> 6 <input type="checkbox"/> 7 <input type="checkbox"/> 8 <input type="checkbox"/> 9 <input type="checkbox"/> 10
3	----	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="text"/> <input type="text"/>	<input type="checkbox"/> 0 <input type="checkbox"/> 1 <input type="checkbox"/> 2 <input type="checkbox"/> 3 <input type="checkbox"/> 4 <input type="checkbox"/> 5 <input type="checkbox"/> 6 <input type="checkbox"/> 7 <input type="checkbox"/> 8 <input type="checkbox"/> 9 <input type="checkbox"/> 10
4	----	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="text"/> <input type="text"/>	<input type="checkbox"/> 0 <input type="checkbox"/> 1 <input type="checkbox"/> 2 <input type="checkbox"/> 3 <input type="checkbox"/> 4 <input type="checkbox"/> 5 <input type="checkbox"/> 6 <input type="checkbox"/> 7 <input type="checkbox"/> 8 <input type="checkbox"/> 9 <input type="checkbox"/> 10
5	----	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="text"/> <input type="text"/>	<input type="checkbox"/> 0 <input type="checkbox"/> 1 <input type="checkbox"/> 2 <input type="checkbox"/> 3 <input type="checkbox"/> 4 <input type="checkbox"/> 5 <input type="checkbox"/> 6 <input type="checkbox"/> 7 <input type="checkbox"/> 8 <input type="checkbox"/> 9 <input type="checkbox"/> 10
6	----	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="text"/> <input type="text"/>	<input type="checkbox"/> 0 <input type="checkbox"/> 1 <input type="checkbox"/> 2 <input type="checkbox"/> 3 <input type="checkbox"/> 4 <input type="checkbox"/> 5 <input type="checkbox"/> 6 <input type="checkbox"/> 7 <input type="checkbox"/> 8 <input type="checkbox"/> 9 <input type="checkbox"/> 10
7	----	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="text"/> <input type="text"/>	<input type="checkbox"/> 0 <input type="checkbox"/> 1 <input type="checkbox"/> 2 <input type="checkbox"/> 3 <input type="checkbox"/> 4 <input type="checkbox"/> 5 <input type="checkbox"/> 6 <input type="checkbox"/> 7 <input type="checkbox"/> 8 <input type="checkbox"/> 9 <input type="checkbox"/> 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	----	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/>	<input type="checkbox"/> 0 <input type="checkbox"/> 1 <input type="checkbox"/> 2 <input type="checkbox"/> 3 <input type="checkbox"/> 4 <input type="checkbox"/> 5 <input type="checkbox"/> 6 <input type="checkbox"/> 7 <input type="checkbox"/> 8 <input type="checkbox"/> 9 <input type="checkbox"/> 10
2	----	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/>	<input type="checkbox"/> 0 <input type="checkbox"/> 1 <input type="checkbox"/> 2 <input type="checkbox"/> 3 <input type="checkbox"/> 4 <input type="checkbox"/> 5 <input type="checkbox"/> 6 <input type="checkbox"/> 7 <input type="checkbox"/> 8 <input type="checkbox"/> 9 <input type="checkbox"/> 10
3	----	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/>	<input type="checkbox"/> 0 <input type="checkbox"/> 1 <input type="checkbox"/> 2 <input type="checkbox"/> 3 <input type="checkbox"/> 4 <input type="checkbox"/> 5 <input type="checkbox"/> 6 <input type="checkbox"/> 7 <input type="checkbox"/> 8 <input type="checkbox"/> 9 <input type="checkbox"/> 10
4	----	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/>	<input type="checkbox"/> 0 <input type="checkbox"/> 1 <input type="checkbox"/> 2 <input type="checkbox"/> 3 <input type="checkbox"/> 4 <input type="checkbox"/> 5 <input type="checkbox"/> 6 <input type="checkbox"/> 7 <input type="checkbox"/> 8 <input type="checkbox"/> 9 <input type="checkbox"/> 10
5	----	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/>	<input type="checkbox"/> 0 <input type="checkbox"/> 1 <input type="checkbox"/> 2 <input type="checkbox"/> 3 <input type="checkbox"/> 4 <input type="checkbox"/> 5 <input type="checkbox"/> 6 <input type="checkbox"/> 7 <input type="checkbox"/> 8 <input type="checkbox"/> 9 <input type="checkbox"/> 10
6	----	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/>	<input type="checkbox"/> 0 <input type="checkbox"/> 1 <input type="checkbox"/> 2 <input type="checkbox"/> 3 <input type="checkbox"/> 4 <input type="checkbox"/> 5 <input type="checkbox"/> 6 <input type="checkbox"/> 7 <input type="checkbox"/> 8 <input type="checkbox"/> 9 <input type="checkbox"/> 10
7	----	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/>	<input type="checkbox"/> 0 <input type="checkbox"/> 1 <input type="checkbox"/> 2 <input type="checkbox"/> 3 <input type="checkbox"/> 4 <input type="checkbox"/> 5 <input type="checkbox"/> 6 <input type="checkbox"/> 7 <input type="checkbox"/> 8 <input type="checkbox"/> 9 <input type="checkbox"/> 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	----	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/>	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> 0 1 2 3 4 5 <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> 6 7 8 9 10
2	----	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/>	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> 0 1 2 3 4 5 <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> 6 7 8 9 10
3	----	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/>	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> 0 1 2 3 4 5 <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> 6 7 8 9 10
4	----	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/>	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> 0 1 2 3 4 5 <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> 6 7 8 9 10
5	----	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/>	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> 0 1 2 3 4 5 <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> 6 7 8 9 10
6	----	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/>	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> 0 1 2 3 4 5 <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> 6 7 8 9 10
7	----	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/>	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> 0 1 2 3 4 5 <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> 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	----	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/>	<input type="checkbox"/> 0 <input type="checkbox"/> 1 <input type="checkbox"/> 2 <input type="checkbox"/> 3 <input type="checkbox"/> 4 <input type="checkbox"/> 5 <input type="checkbox"/> 6 <input type="checkbox"/> 7 <input type="checkbox"/> 8 <input type="checkbox"/> 9 <input type="checkbox"/> 10
2	----	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/>	<input type="checkbox"/> 0 <input type="checkbox"/> 1 <input type="checkbox"/> 2 <input type="checkbox"/> 3 <input type="checkbox"/> 4 <input type="checkbox"/> 5 <input type="checkbox"/> 6 <input type="checkbox"/> 7 <input type="checkbox"/> 8 <input type="checkbox"/> 9 <input type="checkbox"/> 10
3	----	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/>	<input type="checkbox"/> 0 <input type="checkbox"/> 1 <input type="checkbox"/> 2 <input type="checkbox"/> 3 <input type="checkbox"/> 4 <input type="checkbox"/> 5 <input type="checkbox"/> 6 <input type="checkbox"/> 7 <input type="checkbox"/> 8 <input type="checkbox"/> 9 <input type="checkbox"/> 10
4	----	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/>	<input type="checkbox"/> 0 <input type="checkbox"/> 1 <input type="checkbox"/> 2 <input type="checkbox"/> 3 <input type="checkbox"/> 4 <input type="checkbox"/> 5 <input type="checkbox"/> 6 <input type="checkbox"/> 7 <input type="checkbox"/> 8 <input type="checkbox"/> 9 <input type="checkbox"/> 10
5	----	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/>	<input type="checkbox"/> 0 <input type="checkbox"/> 1 <input type="checkbox"/> 2 <input type="checkbox"/> 3 <input type="checkbox"/> 4 <input type="checkbox"/> 5 <input type="checkbox"/> 6 <input type="checkbox"/> 7 <input type="checkbox"/> 8 <input type="checkbox"/> 9 <input type="checkbox"/> 10
6	----	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/>	<input type="checkbox"/> 0 <input type="checkbox"/> 1 <input type="checkbox"/> 2 <input type="checkbox"/> 3 <input type="checkbox"/> 4 <input type="checkbox"/> 5 <input type="checkbox"/> 6 <input type="checkbox"/> 7 <input type="checkbox"/> 8 <input type="checkbox"/> 9 <input type="checkbox"/> 10
7	----	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/>	<input type="checkbox"/> 0 <input type="checkbox"/> 1 <input type="checkbox"/> 2 <input type="checkbox"/> 3 <input type="checkbox"/> 4 <input type="checkbox"/> 5 <input type="checkbox"/> 6 <input type="checkbox"/> 7 <input type="checkbox"/> 8 <input type="checkbox"/> 9 <input type="checkbox"/> 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 treatment	Blood Pressure (mmHg)	Pain (check the number that best represents the maximum pain you experience during the session, if any)
1	----	AM	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/>	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> 0 1 2 3 4 5 <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> 6 7 8 9 10
		PM	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/>	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> 0 1 2 3 4 5 <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> 6 7 8 9 10
2		AM	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/>	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> 0 1 2 3 4 5 <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> 6 7 8 9 10
		PM	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/>	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> 0 1 2 3 4 5 <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> 6 7 8 9 10
3		AM	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/>	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> 0 1 2 3 4 5 <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> 6 7 8 9 10
		PM	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/>	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> 0 1 2 3 4 5 <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> 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 treatment	Blood Pressure (mmHg)	Pain (check the number that best represents the maximum pain you experience during the session, if any)
4	---	AM	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/>	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> 0 1 2 3 4 5 <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> 6 7 8 9 10
		PM	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/>	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> 0 1 2 3 4 5 <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> 6 7 8 9 10
5	---	AM	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/>	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> 0 1 2 3 4 5 <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> 6 7 8 9 10
		PM	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/>	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> 0 1 2 3 4 5 <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> 6 7 8 9 10
6	---	AM	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/>	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> 0 1 2 3 4 5 <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> 6 7 8 9 10
		PM	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/>	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> 0 1 2 3 4 5 <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> 6 7 8 9 10
7	---	AM	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/>	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> 0 1 2 3 4 5 <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> 6 7 8 9 10
		PM	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/>	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> 0 1 2 3 4 5 <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> 6 7 8 9 10





CRU #044 TRIC VCI

Plate #037

Follow Up

Subject ID:

<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>
Centre		Subject ID	

Date:

<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>
yyyy				mm		dd

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

Date that the week started on:

<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>
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 treatment	Blood Pressure (mmHg)	Pain (check the number that best repre- sents the maximum pain you experience during the session, if any)																								
1	----	AM	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/>	<table border="0"> <tr> <td><input type="checkbox"/></td><td><input type="checkbox"/></td><td><input type="checkbox"/></td><td><input type="checkbox"/></td><td><input type="checkbox"/></td><td><input type="checkbox"/></td> </tr> <tr> <td>0</td><td>1</td><td>2</td><td>3</td><td>4</td><td>5</td> </tr> <tr> <td><input type="checkbox"/></td><td><input type="checkbox"/></td><td><input type="checkbox"/></td><td><input type="checkbox"/></td><td><input type="checkbox"/></td><td><input type="checkbox"/></td> </tr> <tr> <td>6</td><td>7</td><td>8</td><td>9</td><td>10</td><td></td> </tr> </table>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	0	1	2	3	4	5	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	6	7	8	9	10	
		<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>																								
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PM	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/>	<table border="0"> <tr> <td><input type="checkbox"/></td><td><input type="checkbox"/></td><td><input type="checkbox"/></td><td><input type="checkbox"/></td><td><input type="checkbox"/></td><td><input type="checkbox"/></td> </tr> <tr> <td>0</td><td>1</td><td>2</td><td>3</td><td>4</td><td>5</td> </tr> <tr> <td><input type="checkbox"/></td><td><input type="checkbox"/></td><td><input type="checkbox"/></td><td><input type="checkbox"/></td><td><input type="checkbox"/></td><td><input type="checkbox"/></td> </tr> <tr> <td>6</td><td>7</td><td>8</td><td>9</td><td>10</td><td></td> </tr> </table>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	0	1	2	3	4	5	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	6	7	8	9	10		
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6	7	8	9	10																											
2		AM	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/>	<table border="0"> <tr> <td><input type="checkbox"/></td><td><input type="checkbox"/></td><td><input type="checkbox"/></td><td><input type="checkbox"/></td><td><input type="checkbox"/></td><td><input type="checkbox"/></td> </tr> <tr> <td>0</td><td>1</td><td>2</td><td>3</td><td>4</td><td>5</td> </tr> <tr> <td><input type="checkbox"/></td><td><input type="checkbox"/></td><td><input type="checkbox"/></td><td><input type="checkbox"/></td><td><input type="checkbox"/></td><td><input type="checkbox"/></td> </tr> <tr> <td>6</td><td>7</td><td>8</td><td>9</td><td>10</td><td></td> </tr> </table>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	0	1	2	3	4	5	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	6	7	8	9	10	
		<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>																								
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<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>																										
6	7	8	9	10																											
PM	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/>	<table border="0"> <tr> <td><input type="checkbox"/></td><td><input type="checkbox"/></td><td><input type="checkbox"/></td><td><input type="checkbox"/></td><td><input type="checkbox"/></td><td><input type="checkbox"/></td> </tr> <tr> <td>0</td><td>1</td><td>2</td><td>3</td><td>4</td><td>5</td> </tr> <tr> <td><input type="checkbox"/></td><td><input type="checkbox"/></td><td><input type="checkbox"/></td><td><input type="checkbox"/></td><td><input type="checkbox"/></td><td><input type="checkbox"/></td> </tr> <tr> <td>6</td><td>7</td><td>8</td><td>9</td><td>10</td><td></td> </tr> </table>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	0	1	2	3	4	5	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	6	7	8	9	10		
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<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>																										
6	7	8	9	10																											
3		AM	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/>	<table border="0"> <tr> <td><input type="checkbox"/></td><td><input type="checkbox"/></td><td><input type="checkbox"/></td><td><input type="checkbox"/></td><td><input type="checkbox"/></td><td><input type="checkbox"/></td> </tr> <tr> <td>0</td><td>1</td><td>2</td><td>3</td><td>4</td><td>5</td> </tr> <tr> <td><input type="checkbox"/></td><td><input type="checkbox"/></td><td><input type="checkbox"/></td><td><input type="checkbox"/></td><td><input type="checkbox"/></td><td><input type="checkbox"/></td> </tr> <tr> <td>6</td><td>7</td><td>8</td><td>9</td><td>10</td><td></td> </tr> </table>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	0	1	2	3	4	5	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	6	7	8	9	10	
		<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>																								
0	1	2	3	4	5																										
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6	7	8	9	10																											
PM	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/>	<table border="0"> <tr> <td><input type="checkbox"/></td><td><input type="checkbox"/></td><td><input type="checkbox"/></td><td><input type="checkbox"/></td><td><input type="checkbox"/></td><td><input type="checkbox"/></td> </tr> <tr> <td>0</td><td>1</td><td>2</td><td>3</td><td>4</td><td>5</td> </tr> <tr> <td><input type="checkbox"/></td><td><input type="checkbox"/></td><td><input type="checkbox"/></td><td><input type="checkbox"/></td><td><input type="checkbox"/></td><td><input type="checkbox"/></td> </tr> <tr> <td>6</td><td>7</td><td>8</td><td>9</td><td>10</td><td></td> </tr> </table>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	0	1	2	3	4	5	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	6	7	8	9	10		
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>																										
0	1	2	3	4	5																										
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>																										
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 treatment	Blood Pressure (mmHg)	Pain (check the number that best represents the maximum pain you experience during the session, if any)
4	---	AM	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/>	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> 0 1 2 3 4 5 <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> 6 7 8 9 10
		PM	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/>	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> 0 1 2 3 4 5 <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> 6 7 8 9 10
5	---	AM	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/>	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> 0 1 2 3 4 5 <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> 6 7 8 9 10
		PM	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/>	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> 0 1 2 3 4 5 <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> 6 7 8 9 10
6	---	AM	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/>	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> 0 1 2 3 4 5 <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> 6 7 8 9 10
		PM	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/>	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> 0 1 2 3 4 5 <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> 6 7 8 9 10
7	---	AM	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/>	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> 0 1 2 3 4 5 <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> 6 7 8 9 10
		PM	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/>	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> 0 1 2 3 4 5 <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> 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 treatment	Blood Pressure (mmHg)	Pain (check the number that best represents the maximum pain you experience during the session, if any)
1	----	AM	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/>	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> 0 1 2 3 4 5 <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> 6 7 8 9 10
		PM	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/>	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> 0 1 2 3 4 5 <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> 6 7 8 9 10
2		AM	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/>	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> 0 1 2 3 4 5 <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> 6 7 8 9 10
		PM	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/>	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> 0 1 2 3 4 5 <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> 6 7 8 9 10
3		AM	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/>	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> 0 1 2 3 4 5 <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> 6 7 8 9 10
		PM	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/>	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> 0 1 2 3 4 5 <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> 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 treatment	Blood Pressure (mmHg)	Pain (check the number that best represents the maximum pain you experience during the session, if any)
4	---	AM	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/>	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> 0 1 2 3 4 5 <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> 6 7 8 9 10
		PM	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/>	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> 0 1 2 3 4 5 <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> 6 7 8 9 10
5	---	AM	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/>	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> 0 1 2 3 4 5 <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> 6 7 8 9 10
		PM	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/>	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> 0 1 2 3 4 5 <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> 6 7 8 9 10
6	---	AM	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/>	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> 0 1 2 3 4 5 <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> 6 7 8 9 10
		PM	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/>	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> 0 1 2 3 4 5 <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> 6 7 8 9 10
7	---	AM	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/>	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> 0 1 2 3 4 5 <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> 6 7 8 9 10
		PM	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/>	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> 0 1 2 3 4 5 <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> 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	<input type="checkbox"/> I took the whole treatment	<input type="checkbox"/> I started but did not	<input type="checkbox"/> 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	----	AM	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/>	<input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> 0 1 2 3 4 5 <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> 6 7 8 9 10
		PM	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/>	<input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> 0 1 2 3 4 5 <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> 6 7 8 9 10
2		AM	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/>	<input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> 0 1 2 3 4 5 <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> 6 7 8 9 10
		PM	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/>	<input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> 0 1 2 3 4 5 <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> 6 7 8 9 10
3		AM	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/>	<input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> 0 1 2 3 4 5 <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> 6 7 8 9 10
		PM	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/>	<input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> 0 1 2 3 4 5 <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> 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	<input checked="" type="checkbox"/> I took the whole treatment	<input type="checkbox"/> I started but did not <input checked="" type="checkbox"/>	<input type="checkbox"/> I missed the treatment	Blood Pressure (mmHg)	Pain (check the number that best represents the maximum pain you experience during the session, if any)
4	----	AM	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/>	<input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> 0 1 2 3 4 5 <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> 6 7 8 9 10
		PM	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/>	<input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> 0 1 2 3 4 5 <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> 6 7 8 9 10
5	----	AM	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/>	<input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> 0 1 2 3 4 5 <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> 6 7 8 9 10
		PM	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/>	<input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> 0 1 2 3 4 5 <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> 6 7 8 9 10
6	----	AM	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/>	<input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> 0 1 2 3 4 5 <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> 6 7 8 9 10
		PM	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/>	<input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> 0 1 2 3 4 5 <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> 6 7 8 9 10
7	----	AM	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/>	<input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> 0 1 2 3 4 5 <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> 6 7 8 9 10
		PM	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/>	<input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> 0 1 2 3 4 5 <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> 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	<input type="checkbox"/> I took the whole treatment	<input type="checkbox"/> I started but did not	<input type="checkbox"/> 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	----	AM	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/>	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> 0 1 2 3 4 5 <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> 6 7 8 9 10
		PM	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/>	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> 0 1 2 3 4 5 <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> 6 7 8 9 10
2		AM	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/>	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> 0 1 2 3 4 5 <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> 6 7 8 9 10
		PM	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/>	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> 0 1 2 3 4 5 <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> 6 7 8 9 10
3		AM	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/>	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> 0 1 2 3 4 5 <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> 6 7 8 9 10
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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	<input checked="" type="checkbox"/> I took the whole treatment	<input type="checkbox"/> I started but did not <input checked="" type="checkbox"/>	<input type="checkbox"/> I missed the treatment	Blood Pressure (mmHg)	Pain (check the number that best represents the maximum pain you experience during the session, if any)
4	----	AM	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/>	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> 0 1 2 3 4 5 <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> 6 7 8 9 10
		PM	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/>	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> 0 1 2 3 4 5 <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> 6 7 8 9 10
5	----	AM	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/>	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> 0 1 2 3 4 5 <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> 6 7 8 9 10
		PM	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/>	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> 0 1 2 3 4 5 <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> 6 7 8 9 10
6	----	AM	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/>	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> 0 1 2 3 4 5 <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> 6 7 8 9 10
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7	----	AM	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/>	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> 0 1 2 3 4 5 <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> 6 7 8 9 10
		PM	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/>	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> 0 1 2 3 4 5 <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> 6 7 8 9 10





CRU #044 TRIC VCI

Plate #045

Randomization

Subject ID:

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Centre

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Subject ID

Date:

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y y y y

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m m

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d d

RANDOMIZATION

Was informed consent obtained?	<input type="checkbox"/> Yes	<input type="checkbox"/> No
Is the participant eligible for randomization?	<input type="checkbox"/> Yes	<input type="checkbox"/> No
Randomization assignment	<input type="checkbox"/> Once Daily Treatment	<input type="checkbox"/> Twice Daily Treatment

Signature: _____	Date: <table border="1" style="display: inline-table; vertical-align: middle;"> <tr> <td style="width: 20px; height: 20px;"></td> <td style="width: 20px; height: 20px;"></td> <td style="width: 20px; height: 20px;"></td> <td style="width: 20px; height: 20px;"></td> </tr> </table> <table border="1" style="display: inline-table; vertical-align: middle; margin-left: 10px;"> <tr> <td style="width: 20px; height: 20px;"></td> <td style="width: 20px; height: 20px;"></td> </tr> </table> <table border="1" style="display: inline-table; vertical-align: middle; margin-left: 10px;"> <tr> <td style="width: 20px; height: 20px;"></td> <td style="width: 20px; height: 20px;"></td> </tr> </table>								





CRU #044 TRIC VCI

Plate #046

Phone Follow Up

Subject ID:

Centre

Subject ID

Date:

y y y y

m m

d d

DAY 2 PHONE VISIT

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

5. Complete the visit checklist:	
Review device instructions	<input type="checkbox"/>
Review diary instructions	<input type="checkbox"/>

COMMENTS (optional)

Signature: _____	Date: <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/>
	y y y y m m d d



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):	<input type="checkbox"/> Yes	<input type="checkbox"/> No
2. Has the subject attempted to use the device:	<input type="checkbox"/> Yes	<input type="checkbox"/> No
3. Does the subject report any problems with using the device:	<input type="checkbox"/> Yes	<input type="checkbox"/> No
4. Is the subject willing to continue to participate in the study:	<input type="checkbox"/> Yes	<input type="checkbox"/> No

5. Complete the visit checklist:

Review device instructions	<input type="checkbox"/>
Review diary instructions	<input type="checkbox"/>

COMMENTS (optional)

Signature: _____ Date:
yyyy mm dd





CRU #044 TRIC VCI

Plate #048

Follow Up

Subject ID:

Centre

Subject ID

Date:

yyyy

mm

dd

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:

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 #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	<input type="checkbox"/>
Retrieve patient diary	<input type="checkbox"/>

Signature: _____ Date:

yyyy mm dd



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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:	<input type="checkbox"/> Yes	<input type="checkbox"/> No	<input type="checkbox"/> Other: _____
Trail-making part A time to completion (seconds):	<input type="text"/> <input type="text"/> <input type="text"/>		
Trail-making part B completed:	<input type="checkbox"/> Yes	<input type="checkbox"/> No	<input type="checkbox"/> Other: _____
Trail-making part B time to completion (seconds):	<input type="text"/> <input type="text"/> <input type="text"/>		
10-item word list learning completed:	<input type="checkbox"/> Yes	<input type="checkbox"/> No	<input type="checkbox"/> Other: _____
Trial 1 immediate recall:	<input type="text"/> <input type="text"/>		
Trial 1 intrusions:	<input type="text"/> <input type="text"/>		
Trial 2 immediate recall:	<input type="text"/> <input type="text"/>		
Trial 2 intrusions:	<input type="text"/> <input type="text"/>		
Trial 3 immediate recall:	<input type="text"/> <input type="text"/>		
Trial 3 intrusions:	<input type="text"/> <input type="text"/>		
Letter A fluency completed:	<input type="checkbox"/> Yes	<input type="checkbox"/> No	<input type="checkbox"/> Other: _____
Letter A fluency number of words:	<input type="text"/> <input type="text"/>		
Letter S fluency completed:	<input type="checkbox"/> Yes	<input type="checkbox"/> No	<input type="checkbox"/> Other: _____
Letter S fluency number of words:	<input type="text"/> <input type="text"/>		
Animal fluency completed:	<input type="checkbox"/> Yes	<input type="checkbox"/> No	<input type="checkbox"/> Other: _____
Animal fluency number of words:	<input type="text"/> <input type="text"/>		





CRU #044 TRIC VCI Plate #052

Randomization End
 Follow Up

Subject ID:
Centre Subject ID

Date:
y y y y m m d d

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:
y y y y m m d d





CRU #044 TRIC VCI

Plate #053

Randomization End

Follow Up

Subject ID:

<i>Centre</i>		<i>Subject ID</i>	

Date:

<i>y y y y</i>				<i>m m</i>		<i>d d</i>

MRI TRANSMITTAL

Date of MRI:	<table border="1" style="width: 100%;"> <tr> <td style="width: 20px; height: 20px;"></td> <td style="width: 20px; height: 20px;"></td> <td style="width: 20px; height: 20px;"></td> <td style="width: 20px; height: 20px;"></td> <td style="width: 20px; height: 20px;"></td> <td style="width: 20px; height: 20px;"></td> <td style="width: 20px; height: 20px;"></td> </tr> <tr> <td colspan="4" style="text-align: center;"><i>y y y y</i></td> <td colspan="2" style="text-align: center;"><i>m m</i></td> <td colspan="1" style="text-align: center;"><i>d d</i></td> </tr> </table>								<i>y y y y</i>				<i>m m</i>		<i>d d</i>
<i>y y y y</i>				<i>m m</i>		<i>d d</i>									
MRI transmitted:	<input type="checkbox"/> Yes <input type="checkbox"/> No														
If no, give reason:															
<input type="checkbox"/> No longer participating in the study (study termination CRF should also have been completed)															
<input type="checkbox"/> Participant declined															
<input type="checkbox"/> Not completed due to claustrophobia															
<input type="checkbox"/> MRI contraindication															
<input type="checkbox"/> MRI technical problem															
<input type="checkbox"/> Other reason: _____															

Signature: _____	Date: <table border="1" style="display: inline-table; vertical-align: middle;"> <tr> <td style="width: 20px; height: 20px;"></td> <td style="width: 20px; height: 20px;"></td> <td style="width: 20px; height: 20px;"></td> <td style="width: 20px; height: 20px;"></td> </tr> <tr> <td colspan="4" style="text-align: center;"><i>y y y y</i></td> </tr> </table> <table border="1" style="display: inline-table; vertical-align: middle; margin-left: 10px;"> <tr> <td style="width: 20px; height: 20px;"></td> <td style="width: 20px; height: 20px;"></td> </tr> <tr> <td colspan="2" style="text-align: center;"><i>m m</i></td> </tr> </table> <table border="1" style="display: inline-table; vertical-align: middle; margin-left: 10px;"> <tr> <td style="width: 20px; height: 20px;"></td> <td style="width: 20px; height: 20px;"></td> </tr> <tr> <td colspan="2" style="text-align: center;"><i>d d</i></td> </tr> </table>					<i>y y y y</i>						<i>m m</i>				<i>d d</i>	
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<i>m m</i>																	
<i>d d</i>																	





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 # <input type="text"/>	Adverse Event term _____		
AE Start Date:	<input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> yyyy	<input type="text"/> <input type="text"/> mm	<input type="text"/> <input type="text"/> dd
AE End Date (or Continuing):	<input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> yyyy	<input type="text"/> <input type="text"/> mm	<input type="text"/> <input type="text"/> dd
Outcome:	<input type="checkbox"/> Fatal	<input type="checkbox"/> Not recovered/ not resolved	<input type="checkbox"/> Recovered w/sequelae
	<input type="checkbox"/> Recovered w/o sequelae	<input type="checkbox"/> Recovering/ resolving	
Severity/Grade:	<input type="checkbox"/> Mild	<input type="checkbox"/> Moderate	<input type="checkbox"/> Severe
Is the Event Serious?	<input type="checkbox"/> Yes (Complete SAE)	<input type="checkbox"/> No	
Is the Event Expected?	<input type="checkbox"/> Yes	<input type="checkbox"/> No	
AE Treatment:	<input type="checkbox"/> None	<input type="checkbox"/> Medication(s)	<input type="checkbox"/> Non-medication TX
Action Taken with Study Intervention:	<input type="checkbox"/> None	<input type="checkbox"/> Interrupted	<input type="checkbox"/> Discontinued
	<input type="checkbox"/> Device sessions reduced	<input type="checkbox"/> Device sessions increased	<input type="checkbox"/> Not Applicable
Attribution/Relatedness:	<input type="checkbox"/> Definite	<input type="checkbox"/> Probable	<input type="checkbox"/> Possible
	<input type="checkbox"/> Unlikely	<input type="checkbox"/> 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 # <input type="text"/>	Site Adverse Event term
	Common sense Adverse Event term
AE Category: (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 # <input type="text"/>	Serious Adverse Event term _____
Report Type	<input type="checkbox"/> Initial Report <input type="checkbox"/> Follow-up Report F/U Report # <input type="text"/> <input type="checkbox"/> Final Report
SAE Classification:	<input type="checkbox"/> Fatal (resulted in death)
	<input type="checkbox"/> A life-threatening occurrence
	<input type="checkbox"/> Requires inpatient hospitalization or prolongation of existing hospitalization
	<input type="checkbox"/> Results in persistent or significant disability/incapacity
	<input type="checkbox"/> Results in congenital anomaly/birth defect
	<input type="checkbox"/> 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.
	<input type="checkbox"/> 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:	<input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> yyyy <input type="text"/> <input type="text"/> mm <input type="text"/> <input type="text"/> dd
SAE End Date (or Continuing):	<input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> yyyy <input type="text"/> <input type="text"/> mm <input type="text"/> <input type="text"/> dd <input type="checkbox"/> Continuing
Grade:	<input type="checkbox"/> Mild <input type="checkbox"/> Moderate <input type="checkbox"/> Severe <input type="checkbox"/> Life Threatening <input type="checkbox"/> Death (Fatal)
Is the Event Expected?	<input type="checkbox"/> Yes <input type="checkbox"/> 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:	<input type="checkbox"/> Definite	<input type="checkbox"/> Probable	<input type="checkbox"/> Possible
	<input type="checkbox"/> Unlikely	<input type="checkbox"/> Unrelated	
Outcome:	<input type="checkbox"/> Fatal	<input type="checkbox"/> Not recovered/ not resolved	<input type="checkbox"/> Recovered w/sequelae
	<input type="checkbox"/> Recovered w/o sequelae	<input type="checkbox"/> Recovering/ resolving	
Lead Site Notified Date:	<input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/>	<input type="text"/> <input type="text"/>	<input type="text"/> <input type="text"/>
	y y y y	m m	d d
Local IRB/REB Notified Date:	<input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/>	<input type="text"/> <input type="text"/>	<input type="text"/> <input type="text"/>
	y y y y	m m	d d
Narrative/Details:	<hr/>		

Signature of investigator confirms 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:

Review only





CRU #044 TRIC VCI

Plate #061

Pg#:

Subject ID:

Centre

Subject ID

Date:

y y y y

m m

d d

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: _____

Review only





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: <input type="text"/> <input type="text"/> <input type="text"/> . <input type="text"/> <input type="text"/>
Indication: _____	Units: <input type="checkbox"/> mg <input type="checkbox"/> mcg <input type="checkbox"/> mL <input type="checkbox"/> cc <input type="checkbox"/> IU <input type="checkbox"/> mEq <input type="checkbox"/> oz <input type="checkbox"/> tsp <input type="checkbox"/> tbl <input type="checkbox"/> gtt
Route:	<input type="checkbox"/> po <input type="checkbox"/> pr <input type="checkbox"/> sub-q <input type="checkbox"/> sub-lingual <input type="checkbox"/> IM <input type="checkbox"/> IV <input type="checkbox"/> Patch <input type="checkbox"/> Topical <input type="checkbox"/> Nasal <input type="checkbox"/> Other: _____
Frequency:	<input type="checkbox"/> OD <input type="checkbox"/> BID <input type="checkbox"/> TID <input type="checkbox"/> QID <input type="checkbox"/> PRN <input type="checkbox"/> Other: _____
Start Date:	<input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/>
End Date:	<input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> OR <input type="checkbox"/> Unable to determine

Medication Name: _____	Dose: <input type="text"/> <input type="text"/> <input type="text"/> . <input type="text"/> <input type="text"/>
Indication: _____	Units: <input type="checkbox"/> mg <input type="checkbox"/> mcg <input type="checkbox"/> mL <input type="checkbox"/> cc <input type="checkbox"/> IU <input type="checkbox"/> mEq <input type="checkbox"/> oz <input type="checkbox"/> tsp <input type="checkbox"/> tbl <input type="checkbox"/> gtt
Route:	<input type="checkbox"/> po <input type="checkbox"/> pr <input type="checkbox"/> sub-q <input type="checkbox"/> sub-lingual <input type="checkbox"/> IM <input type="checkbox"/> IV <input type="checkbox"/> Patch <input type="checkbox"/> Topical <input type="checkbox"/> Nasal <input type="checkbox"/> Other: _____
Frequency:	<input type="checkbox"/> OD <input type="checkbox"/> BID <input type="checkbox"/> TID <input type="checkbox"/> QID <input type="checkbox"/> PRN <input type="checkbox"/> Other: _____
Start Date:	<input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/>
End Date:	<input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> OR <input type="checkbox"/> Unable to determine

Signature: _____ Date:





CRU #044 TRIC VCI

Plate #063

Randomization

Subject ID:

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Centre

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Subject ID

Date:

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DEVICE PROVISION

1. Randomization and device provision checklist:	<input type="checkbox"/> Subject randomized				
	<input type="checkbox"/> Device provided				
	<input type="checkbox"/> Device instructions provided				
	<input type="checkbox"/> Subject diary provided				
	<input type="checkbox"/> Device training provided				
2. First treatment cycle:	<input type="checkbox"/> Completed	<input type="checkbox"/> 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:	<table border="1" style="display: inline-table; vertical-align: middle;"> <tr> <td style="width: 20px; height: 20px;"></td> <td style="width: 20px; height: 20px;"></td> </tr> </table> [range 0-10]			
	3.b. Pain level during the last cuff inflation of the cycle:	<table border="1" style="display: inline-table; vertical-align: middle;"> <tr> <td style="width: 20px; height: 20px;"></td> <td style="width: 20px; height: 20px;"></td> </tr> </table> [range 0-10]			
4. Symptoms reported during treatment (check all that apply):					
Was the treatment painful?	<input type="checkbox"/> Yes	<input type="checkbox"/> No	<input type="checkbox"/> Not sure		
Was there tingling (paresthesia)?	<input type="checkbox"/> Yes	<input type="checkbox"/> No	<input type="checkbox"/> Not sure		
5. Other symptoms during treatment:					
6. Is subject willing to continue in the study:	<input type="checkbox"/> Yes	<input type="checkbox"/> No			
If "No", then subject will not continue in the study. Complete CRF Study Drop Out.					
Signature: _____	Date: _____				
	y y y y m m d d				



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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

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3 All study investigators at the clinical sites must ensure that the confidentiality of personal
4 identity and all personal medical information of study participants are maintained at all
5 times. Federal legislation in Canada (Personal Information Protection and Electronic
6 Documents Act [PIPEDA]), and provincial legislation (eg. Health Information Act [HIA in
7 Alberta) where applicable, must be followed. Additionally, any U.S. clinical sites must follow
8 privacy obligations to study participants under the Health Insurance Portability and
9 Accountability Act (HIPAA). European or Asian/Australasian sites must conform to local
10 privacy and confidentiality law and custom. On the CRFs and other study documents or
11 image materials submitted to the CRU, the subjects are identified only by study
12 identification code.
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20 Personal medical information may be reviewed for the purpose of verifying data recorded
21 in the CRF by the site monitors. Other properly authorized persons, such as the regulatory
22 authorities, may also have access to these records. Personal medical information is
23 always treated as confidential.
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26

27 **Audit and inspection**

28
29 The Sponsor-Investigator and any Participating Site Investigators should understand that
30 source documents for this trial should be made available to appropriately qualified
31 personnel from the Sponsor-Investigator or designee after appropriate notification. The
32 verification of the CRF data must be by direct inspection of source documents.
33
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35
36

37 Any Participating Site Investigators shall supply the Sponsor-Investigator on request with
38 any required background data from the study documentation or clinic records. This is
39 particularly important when CRFs are illegible or when errors in data transcription are
40 suspected. In case of special problems and/or governmental queries or requests for audit
41 inspections, it is also necessary to have access to the complete study records, provided
42 that subject confidentiality is protected.
43
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48 **Archiving**

49 The Sponsor-Investigator (and any Participating Site Investigators) must keep both (1)

50
51 [REDACTED] J [REDACTED] 6 [REDACTED] O [REDACTED] [REDACTED] [REDACTED] M [REDACTED] F [REDACTED] F O [REDACTED]
52
53 clinical trial regulation. For example, at the University of Calgary, for non-Health Canada
54 regulated studies, that period is 5 years from the time of official closure of the study. After that
55 period of time the documents may be destroyed, subject to local regulations.
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5 Data sharing policies will follow the spirit of the National Institute of Health (NIH) policy
6 [\[http://grants2.nih.gov/grants/policy/data_sharing/data_sharing_guidance.htm\]](http://grants2.nih.gov/grants/policy/data_sharing/data_sharing_guidance.htm). A similar
7
8 policy is in place at the Canadian Institutes of Health Research (CIHR). In addition, the
9
10 Executive Committee will follow the CIHR guidelines on public access to trial results and
11 make the results available as free-access using PubMed. Upon completion of the trial, a
12
13 public use database will be prepared by stripping any and all personal identifiers. The
14
15 public use database, consisting of several data files, should contain: (1) baseline and
16
17 demographic characteristics; (2) outcomes assessments; (3) MRI data; (4) cognitive data;
18
19 (5) concomitant medications; and (6) adverse events. Each data file is made available as a
20
21 formatted text file or other electronic format. The data files are distributed along with the
22
23 available to the public one year after completion of follow-up for the last subject.



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

1 **Introduction**

2

3 Background and 6a Description of research question and justification for undertaking the trial, including summary of relevant _____5-7_____

4 rationale studies (published and unpublished) examining benefits and harms for each intervention

5

6 6b Explanation for choice of comparators _____7_____

7

8 Objectives 7 Specific objectives or hypotheses _____7_____

9

10 Trial design 8 Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group),

11 allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory) _____8_____

12

13

14 **Methods: Participants, interventions, and outcomes**

15

16 Study setting 9 Description of study settings (eg, community clinic, academic hospital) and list of countries where data will _____13_____

17 be collected. Reference to where list of study sites can be obtained

18

19 Eligibility criteria 10 Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and _____10_____

20 individuals who will perform the interventions (eg, surgeons, psychotherapists)

21

22 Interventions 11a Interventions for each group with sufficient detail to allow replication, including how and when they will be _____8-9_____

23 administered

24

25 11b Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose _____9_____

26 change in response to harms, participant request, or improving/worsening disease)

27

28 11c Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence _____11_____

29 (eg, drug tablet return, laboratory tests)

30

31 11d Relevant concomitant care and interventions that are permitted or prohibited during the trial _____10_____

32

33

34 Outcomes 12 Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood _____12_____

35 pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, _____12_____

36 median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen

37 efficacy and harm outcomes is strongly recommended

38

39

40 Participant timeline 13 Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for _____12_____

41 participants. A schematic diagram is highly recommended (see Figure)

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1	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_____
2				
3				
4	Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	_____12_____
5				

6 **Methods: Assignment of interventions (for controlled trials)**

7 Allocation:

8				
9				
10	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_____
11				
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16	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_____
17				
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20	Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	_____16_____
21				
22				
23				
24	Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	_____9_____
25				
26				
27		17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	_____9_____
28				
29				
30				

31 **Methods: Data collection, management, and analysis**

32				
33	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
34				
35				
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39		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_____
40				
41				
42				

1	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
2				
3				
4				
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___
6				
7				
8		20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	___14___
9				
10		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___
11				
12				
13				
14	Methods: Monitoring			
15				
16	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
17				
18				
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21				
22		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__
23				
24				
25	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___
26				
27				
28	Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	___17___
29				
30				
31				
32	Ethics and dissemination			
33				
34	Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	___16___
35				
36				
37	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___
38				
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1	Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	_____16_____
2				
3				
4		26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	_____16_____
5				
6				
7	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_____
8				
9				
10	Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	_____16_____
11				
12				
13	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_____
14				
15				
16				
17	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_
18				
19				
20	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_____
21				
22				
23				
24		31b	Authorship eligibility guidelines and any intended use of professional writers	_supplement 5
25				
26		31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	_____18_____
27				
28				
29	Appendices			
30				
31	Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	_supplement 4
32				
33				
34	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
35				
36				

*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](https://creativecommons.org/licenses/by-nc-nd/3.0/)" 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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Primary Subject Heading:	Neurology
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Keywords:	Clinical trials < THERAPEUTICS, Dementia < NEUROLOGY, Stroke < NEUROLOGY

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3 **Trial of Remote Ischaemic Pre-Conditioning in Vascular Cognitive Impairment (TRIC-VCI):**
4 **Protocol for a randomised controlled trial**
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7

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5
6
7
8 **Word count:** 3998 excluding abstract, references, tables, figures

9 **Tables:** 3

10
11 **Figures:** 1

12
13 **Supplementary Files:** 5

14
15
16 **Key words:** clinical trial, vascular dementia, remote ischemic conditioning

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For peer review only

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 consist 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 $\geq 80\%$ 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

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3 biomarkers of RIC. Candidate biomarkers include circulating nitrite, heat shock protein 27,
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5 microRNA-144, and interleukin-10.¹³⁻¹⁶
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10 In a bilateral carotid occlusion model of VCI in mice, chronic daily RIC demonstrated increased
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12 angiogenesis (capillary density), cerebral flood flow, and preservation of white matter
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14 myelination at 1-month and 4-months.¹⁷ In humans, RIC has been trialled for percutaneous
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16 coronary intervention (PCI) in the setting of acute myocardial infarction (MI),^{18 19} elective PCI,¹⁹
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18 and cardiac surgery.²⁰ RIC has also been studied in the past few years in cerebrovascular
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20 disease, mostly applied to the upper-limb but some in the lower-limb,²¹⁻²⁶ and in several studies
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22 of peri-/post-conditioning (happening after ischaemic/haemorrhagic injury).²⁷⁻²⁹ Bilateral upper-
23
24 limb RIC protects against recurrent stroke in intracranial arterial stenosis.²² A systematic review
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26 of RIC included three trials (371 participants) for ischaemic stroke prevention and four trials (364
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28 participants) for ischaemic stroke treatment, and found low-quality evidence that RIC reduces
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30 recurrent stroke risk in patients with intracerebral artery stenosis and reduces stroke severity in
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32 patients undergoing carotid stenting.³⁰ There is also preliminary evidence of efficacy for this
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34 therapy in cSVD. A trial of 17 patients with cSVD randomised to RIC or sham-RIC reported
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36 improved mean flow velocity of the middle cerebral artery, lower dizziness handicap inventory
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38 score, and lower post-treatment WMH volume in the RIC group.²³ A trial in 36 patients with
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40 cSVD reported a significant reduction in WMH volume at 1-year compared to sham-RIC and a
41
42 significant difference on visuospatial and executive function sections of the Montreal Cognitive
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44 Assessment (MoCA), though there was no significant change in the number of lacunes.²⁴
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50 Prior studies of RIC in cSVD have been small and essentially hypothesis-generating, and
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52 several uncertainties remain. First, the required “dose” of RIC sessions to observe a favourable
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54 effect is uncertain: a number of published studies have used bilateral upper-arm RIC twice
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56 daily,^{22 24} but if similar results are obtained with once-daily and/or single upper-arm sessions,
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3 this would be especially appealing for patients and facilitate treatment adoption. Importantly,
4 human³¹ and animal model^{32 33} studies show that single-limb RIC with only 3-4 cycles can
5 reduce end-organ ischaemic damage. As there are few human data to guide dose choices, the
6 most comprehensive dose-finding data comes from an animal study³³ which found that more
7 than one limb, more than four cycles, and more than 5-minutes of ischaemia conferred no
8 additional reductions in infarct size in a mouse model of acute MI. Second, most published
9 studies have reported exceptionally high patient compliance (>80%), even with bilateral upper-
10 arm, twice-daily sessions – requiring at least 100-minutes daily, during which they can do little
11 meaningful activity. It is uncertain whether similarly high compliance can be expected in the trial
12 target population of persons with cognitive impairment. Third, the persistence of treatment
13 effects beyond RIC cessation – as suggested by the “late phase” of RIC-related physiological
14 changes per laboratory studies¹⁷ – remains to be demonstrated. The aforementioned mouse
15 model of bilateral carotid occlusion showed similar efficacy of RIC in mice receiving 1-month or
16 4-months of therapy,¹⁷ but it is unclear if such persistence can be seen in humans. Fifth, prior
17 cSVD trials (including of non-RIC treatments) have suffered from common methodological
18 problems including lack of neuroimaging for diagnosis/classification, low-quality trial design (lack
19 of intent-to-treat analysis or pre-specified primary outcomes, failure to account for multiple
20 comparisons), and lack of biomarkers for monitoring and treatment response.³⁴
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43 Therefore, we propose an early phase trial to lay the foundation for a research program to
44 further investigate the effect of RIC on prevention of cognitive decline caused by brain infarction
45 from cSVD. We will examine whether different doses of daily RIC performed for 1-month are
46 tolerable and safe, whether they result in improved cerebral blood flow (CBF), and whether the
47 biomarker effects of 1-month of treatment are sustained at 3-months.
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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

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3 based on adherence during the run-in period) and 30-day visits. The proportion that complete
4 the run-in period will be a secondary endpoint.
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9 **Discontinuation from study treatment**

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

- 13 1. Patient declares unwillingness to proceed with the intervention.
- 14 2. Treatment is interrupted for >48-hours for any reason.
- 15 3. Diagnosis of deep venous thrombosis (DVT) or pulmonary embolism (PE).
- 16 4. Surgery on the upper extremity is performed or clinically indicated prior to cessation of
17 the 30-day active treatment period.
- 18 5. Initiation of anticoagulation is clinically indicated.
- 19 6. Patient develops any other serious adverse event deemed by the attending physician to
20 merit cessation of RIC.
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30 The time-point of discontinuation will be recorded as accurately as possible (using device data)
31 to determine the total number of actual treatment days for each patient. All patients will be
32 followed to the end of the study period and analyzed in their assigned treatment arm.
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39 **Randomisation scheme**

40 All subjects will be enrolled in this study consecutively and randomised into the two treatment
41 groups in a 1:1 ratio. Randomisation will use a web-based algorithm with treatment assignment
42 allocated by web-based real-time interaction with the site. Treatment assignments will be made
43 using the Permuted Blocks method with randomly selected block sizes of 2, 4, or 6.
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51 **Methods for protecting against bias (blinding)**

52 Participant assignments will not be concealed from treating physicians or subjects.
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3 Investigators and assessors responsible for evaluating the results of cognitive testing, activities
4 of daily living (ADLs), neuroimaging, and plasma testing will be blinded to treatment assignment.
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6 After enrolment of each subject, the site will designate a blinded evaluator (declared in the
7
8 randomisation form) to perform 30-day and 90-day follow-up evaluations. This individual cannot
9
10 be involved in the participant's care and must remain blinded to treatment assignment.
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13 Participants will be instructed not to disclose their treatment group to evaluators. Neuroimaging
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15 end-points will be determined by the core imaging laboratory blinded to treatment allocation.
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20 **Inclusion and exclusion criteria**

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22 Full details of the inclusion and exclusion criteria are listed in **Table 1**. Briefly, we will enrol
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24 patients with mild vascular neurocognitive disorder, or the earlier stages of major vascular
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26 neurocognitive disorder. This will include patients with neuroimaging evidence of significant
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28 cSVD burden (as defined in **Table 1**), objective evidence of cognitive impairment (MoCA \leq 24)
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30 but independent in basic ADLs, and for whom concerns regarding cognition are expressed by
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32 the patient, caregiver, or referring clinician. To target patients in the milder range of cognitive
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34 impairment, we will exclude patients with MoCA $<$ 13.
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39 Participants with small cortical infarcts will be allowed but patients with larger ($>$ 10mm axial
40
41 diameter) cortical infarcts will be excluded. This is because large destructive lesions may
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43 confound study assessments of the impact of progressive cSVD by independently causing
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45 clinical disabilities (aphasia, anosognosia, etc) or by confounding neuroimaging processing
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47 pipelines. For similar reasons, we exclude patients with a prior history of stroke-related
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49 disability, who by definition will not meet our inclusion criterion of being independent for basic
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51 ADLs. Whereas all patients will meet inclusion criteria for demonstrating evidence of cSVD on
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53 CT/MRI, we will not require testing for biomarkers of Alzheimer's Disease in our study, with the
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55 understanding that some patients will have mixed dementia.
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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

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3 The primary feasibility/compliance outcomes will be adherence rate at 30 days, defined as the
4 percentage of sessions completed. Secondary safety/tolerability and efficacy endpoints are
5 specified in **Table 2**. The main efficacy endpoints include change in cognitive test scores on the
6 MoCA,³⁶ Trail-Making A and B,³⁷ Controlled Oral Word Association Test (COWAT),^{38 39} and
7 CERAD 10-item word list learning⁴⁰ at 30-days and 90-days, change in MRI peak skeletonized
8 mean diffusivity of the white matter,⁴¹ and change in WMH volume.

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

17 18 19 20 21 22 **Procedures and variables**

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24 The schedule of procedures and variable collection for the trial is presented in **Table 3**.
25
26 Details of study assessments at each visit are presented in **Supplementary File 2**. Cognitive
27 testing and MRI will be done at randomization, 30-days, and 90-days. Each study participant will
28 also have an informant, ideally one who lives with them or is a caregiver, who will provide
29 important collateral data about their cognitive and behavioural status (via the AD8 informant
30 questionnaire, IQCODE, and the MBI checklist) and daily activities (via the Bristol ADL Scale
31 [BADLS] longitudinally).

32 33 34 35 36 37 38 39 40 41 **Sample size justification**

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

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5 Sample size calculations for biomarker efficacy are based on the ability to restore more normal
6 gray matter CBF in patients with VCI due to cSVD. Prior literature on CBF measurements in
7 cSVD has recently been systematically reviewed⁴². Based on a prior study of cSVD VCI
8 patients,⁴³ we estimate gray matter CBF will be 37.8 ± 12.4 mL/100g brain tissue/minute in cSVD
9 and 55.8 ± 12.4 mL/100g/minute in age matched healthy controls. We estimate that RIC will
10 restore 52% of normal CBF (i.e. an increase to 46.8 mL/100g/minute), as seen in an animal
11 model of VCI¹⁷. CBF can be measured with good precision using MRI PCASL (estimated within-
12 subject coefficient of variation 4.1% based on two studies^{44 45}). Based on these assumptions
13 and two-tailed $\alpha=0.05$, the current trial will provide >99% power to detect a mean increase
14 of 9 mL/100g/min CBF from baseline within each arm. For a future phase 2b study, a sample
15 size of 32 in each arm would provide 80% power and a sample size of 42 in each arm would
16 provide 90% power to determine whether RIC increases CBF by 9 mL/100g/minute compared to
17 a sham control. Since this is a relatively novel use of ASL, and our estimate for CBF increase
18 are based on a small study sample with mild dementia,⁴³ our sample size estimation for the
19 biomarker component must be interpreted with caution, and the CBF measure is best
20 interpreted as an exploratory outcome.
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41 **Recruitment strategy and projected recruitment rate**

42 Patients will be screened at specialty Stroke/TIA clinics and Cognitive clinics (generally staffed
43 by neurologists, geriatricians, or psychiatrists) at each of the study sites. The initial screening
44 can be done by clinicians as part of usual care, since a number of the evaluations needed to
45 determine study eligibility (clinical history of cognitive symptoms, MoCA, and neuroimaging) are
46 commonly used clinical tests recommended by Canadian clinical guidelines. We aim for a
47 recruitment rate of 1 patient per month per site (5/month across all sites), aiming to achieve our
48 target sample size of 24 in 7-8 months.
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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 $\geq 80\%$ 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.

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3 For the qualitative exit interview with participants, an audio recording of the group session will
4 be transcribed and analyzed for emerging themes regarding the ease of use of the RIC device,
5 the quality of the user manual and other patient instructions, the tolerability of the treatment, and
6 advice for conduct of future trials.
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11 12 13 **Handling of missing data**

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

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

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

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3 all versions of ethics-approved ICFs, staff curriculum vitae and authorization forms and other
4 appropriate documents/correspondence.
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9 Subject clinical source documents would include subject hospital/clinic records, physician's and
10 nurse's notes, appointment book, original laboratory reports, imaging reports, completed CRFs
11 **(Supplementary File 4)**, any relevant pathology and special assessment reports, signed ICFs,
12 consultant letters, and subject screening and enrolment logs.
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20 For each subject enrolled, a CRF will be completed and signed by the Sponsor-Investigator
21 (and any Participating Site Investigator) or authorized delegate from the study staff. This
22 also applies to records for those patients who fail to complete the study (even during a pre--
23 randomisation screening period if a CRF was initiated). If a subject withdraws from the
24 study, the reason must be noted on a CRF. If a subject is withdrawn from the study because
25 of a treatment-limiting AE, thorough efforts will be made to clearly document the outcome.
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35 **Monitoring**

36 All data will be monitored centrally by the coordinating center at the University of Calgary for
37 accuracy and completeness. The initial performance-monitoring assessment will take place after
38 the initial subject is enrolled, and the next assessment will take place at close-out. The close-out
39 monitoring assessment will take place at completion of subject enrolment and protocol required
40 follow-up visits at the performance site. Monitoring visits will be done remotely by
41 teleconference, but the coordinating center reserves the right to conduct on-site monitoring at its
42 discretion. The monitor will verify the adequacy of site facilities and staff, site recruitment,
43 subject randomisation, ICFs, and the presence of regulatory documents. During the visit, any
44 omissions/corrections to data submitted to the database are noted and queries are generated
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3 by the monitor. At close-out, sites are instructed in the record retention of all trial documents.
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5 PIs will issue a final report to the ethics board.
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10 Details on study coordination, the steering committee, data processing, audit and inspection,
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12 and archiving protocols are presented in **Supplementary File 5**.
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15 16 **Safety and Adverse Events**

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18 Adverse events should be reported as they occur on the CRF. Documentation must be
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20 supported by an entry in the subject's file. Each event should be described in detail along
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22 with start and stop dates, severity, relationship to the therapy as judged by the Investigator,
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24 action taken and outcome. Serious adverse events (SAEs) must be reported within 1
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26 business day of the local investigator or outcome assessor's first awareness of its
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28 occurrence. SAEs will be reviewed by the trial medical monitor. Because this is not a
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30 regulatory trial, SAEs do not require reporting to Health Canada or other regulatory
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32 authorities. Because the adverse event profile of RIC has been quite benign in previous
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34 trials, we do not predict that there will be unexpected SAEs.
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40 Safety outcomes of DVT/PE, arm neurovascular injury, and serious adverse events will be
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42 adjudicated by a medical monitor, an independent neurologist with experience in clinical
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44 trials, who will report these events to the Steering Committee.
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47 48 **Data dissemination**

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50 Results will be disseminated through peer-reviewed publications, professional organisations,
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52 and conferences. The de-identified study dataset and analysis code will be posted to the
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54 University of Calgary section of the PRISM dataverse at the time of publication of the main
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56 study results. The data will complement work by our basic/translational science collaborators
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3 who will be conducting parallel animal studies to explore dose response relationships with
4 various additional RIC regimens in greater granularity – which we are unable to do in our trial for
5 practical reasons of cost and the available patient population.
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9 The data from this trial will be used to inform decisions on study design for a subsequent phase
10 2b trial including: 1) the frequency (once or twice daily) of RIC, based on adherence and safety
11 data, 2) the choice of clinical cognitive and functional tests and assessment scales, based on
12 feasibility and reliability, and 3) the choice of biomarkers, based on feasibility, reliability, and
13 sensitivity to change over time.
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REFERENCES

1. Pantoni L. Cerebral small vessel disease: from pathogenesis and clinical characteristics to therapeutic challenges. *The Lancet Neurology* 2010;9(7):689-701. doi: 10.1016/S1474-4422(10)70104-6
2. Wardlaw JM, Smith EE, Biessels GJ, et al. Neuroimaging standards for research into small vessel disease and its contribution to ageing and neurodegeneration. *The Lancet Neurology* 2013;12(8):822-38. doi: 10.1016/S1474-4422(13)70124-8
3. Schneider JA, Arvanitakis Z, Bang W, et al. Mixed brain pathologies account for most dementia cases in community-dwelling older persons. *Neurology* 2007;69(24):2197-204. doi: 10.1212/01.wnl.0000271090.28148.24
4. Conklin J, Silver FL, Mikulis DJ, et al. Are acute infarcts the cause of leukoaraiosis? Brain mapping for 16 consecutive weeks. *Annals of neurology* 2014;76(6):899-904. doi: 10.1002/ana.24285
5. Kimberly WT, Gilson A, Rost NS, et al. Silent ischemic infarcts are associated with hemorrhage burden in cerebral amyloid angiopathy. *Neurology* 2009;72(14):1230-5. doi: 10.1212/01.wnl.0000345666.83318.03
6. Pavlovic AM, Pekmezovic T, Tomic G, et al. Baseline predictors of cognitive decline in patients with cerebral small vessel disease. *Journal of Alzheimer's disease : JAD* 2014;42 Suppl 3:S37-43. doi: 10.3233/JAD-132606
7. van der Flier WM, van Straaten EC, Barkhof F, et al. Small vessel disease and general cognitive function in nondisabled elderly: the LADIS study. *Stroke* 2005;36(10):2116-20. doi: 10.1161/01.STR.0000179092.59909.42
8. Smith EE, Saposnik G, Biessels GJ, et al. Prevention of Stroke in Patients With Silent Cerebrovascular Disease: A Scientific Statement for Healthcare Professionals From the American Heart Association/American Stroke Association. *Stroke* 2017;48(2):e44-e71. doi: 10.1161/STR.0000000000000116

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3 9. Jia J, Wei C, Liang J, et al. The effects of DL-3-n-butylphthalide in patients with vascular
4 cognitive impairment without dementia caused by subcortical ischemic small vessel
5 disease: A multicentre, randomized, double-blind, placebo-controlled trial. *Alzheimer's &*
6 *dementia : the journal of the Alzheimer's Association* 2016;12(2):89-99. doi:
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8 10.1016/j.jalz.2015.04.010
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13 10. Stokfisz K, Ledakowicz-Polak A, Zagorski M, et al. Ischaemic preconditioning - Current
14 knowledge and potential future applications after 30 years of experience. *Advances in*
15 *medical sciences* 2017;62(2):307-16. doi: 10.1016/j.advms.2016.11.006
16
17
18
19
20 11. Pan J, Li X, Peng Y. Remote ischemic conditioning for acute ischemic stroke: dawn in the
21 darkness. *Reviews in the neurosciences* 2016;27(5):501-10. doi: 10.1515/revneuro-
22 2015-0043
23
24
25
26 12. Berger MM, Macholz F, Mairbaurl H, et al. Remote ischemic preconditioning for prevention
27 of high-altitude diseases: fact or fiction? *Journal of applied physiology*
28 2015;119(10):1143-51. doi: 10.1152/jappphysiol.00156.2015
29
30
31
32 13. Hess DC, Blauenfeldt RA, Andersen G, et al. Remote ischaemic conditioning-a new
33 paradigm of self-protection in the brain. *Nature reviews Neurology* 2015;11(12):698-710.
34 doi: 10.1038/nrneurol.2015.223
35
36
37
38 14. Rassaf T, Totzeck M, Hendgen-Cotta UB, et al. Circulating nitrite contributes to
39 cardioprotection by remote ischemic preconditioning. *Circulation research*
40 2014;114(10):1601-10. doi: 10.1161/CIRCRESAHA.114.303822
41
42
43
44 15. Li J, Rohailla S, Gelber N, et al. MicroRNA-144 is a circulating effector of remote ischemic
45 preconditioning. *Basic research in cardiology* 2014;109(5):423. doi: 10.1007/s00395-
46 014-0423-z
47
48
49
50 16. Cai ZP, Parajuli N, Zheng X, et al. Remote ischemic preconditioning confers late protection
51 against myocardial ischemia-reperfusion injury in mice by upregulating interleukin-10.
52 *Basic research in cardiology* 2012;107(4):277. doi: 10.1007/s00395-012-0277-1
53
54
55
56
57
58
59
60

- 1
2
3 17. Khan MB, Hafez S, Hoda MN, et al. Chronic Remote Ischemic Conditioning Is
4
5 Cerebroprotective and Induces Vascular Remodeling in a VCID Model. *Translational*
6
7 *stroke research* 2018;9(1):51-63. doi: 10.1007/s12975-017-0555-1
8
9
10 18. McLeod SL, Iansavichene A, Cheskes S. Remote ischemic preconditioning to reduce
11
12 reperfusion injury during acute ST-segment-elevation myocardial infarction: A systematic
13
14 review and meta-analysis. *J Am Heart Assoc* 2017;6(5) doi: 10.1161/JAHA.117.005522
15
16 19. Blusztajn DI, Brooks MJ, Andrews DT. A systematic review and meta-analysis evaluating
17
18 ischemic conditioning during percutaneous coronary intervention. *Future Cardiol*
19
20 2017;13(6):579-92. doi: 10.2217/fca-2017-0042
21
22 20. Pierce B, Bole I, Patel V, et al. Clinical outcomes of remote ischemic preconditioning prior to
23
24 cardiac surgery: A meta-analysis of randomized controlled trials. *J Am Heart Assoc*
25
26 2017;6(2) doi: 10.1161/JAHA.116.004666
27
28 21. Meng R, Ding Y, Asmaro K, et al. Ischemic Conditioning Is Safe and Effective for Octo- and
29
30 Nonagenarians in Stroke Prevention and Treatment. *Neurotherapeutics : the journal of*
31
32 *the American Society for Experimental Neurotherapeutics* 2015;12(3):667-77. doi:
33
34 10.1007/s13311-015-0358-6
35
36 22. Meng R, Asmaro K, Meng L, et al. Upper limb ischemic preconditioning prevents recurrent
37
38 stroke in intracranial arterial stenosis. *Neurology* 2012;79(18):1853-61. doi:
39
40 10.1212/WNL.0b013e318271f76a
41
42 23. Mi T, Yu F, Ji X, et al. The Interventional Effect of Remote Ischemic Preconditioning on
43
44 Cerebral Small Vessel Disease: A Pilot Randomized Clinical Trial. *European neurology*
45
46 2016;76(1-2):28-34. doi: 10.1159/000447536
47
48 24. Wang Y, Meng R, Song H, et al. Remote Ischemic Conditioning May Improve Outcomes of
49
50 Patients With Cerebral Small-Vessel Disease. *Stroke* 2017;48(11):3064-72. doi:
51
52 10.1161/STROKEAHA.117.017691
53
54
55
56
57
58
59
60

- 1
2
3 25. Bilgin-Freiert A, Dusick JR, Stein NR, et al. Muscle microdialysis to confirm sublethal
4
5 ischemia in the induction of remote ischemic preconditioning. *Translational stroke*
6
7 *research* 2012;3(2):266-72. doi: 10.1007/s12975-012-0153-1
8
- 9
10 26. Zhao W, Meng R, Ma C, et al. Safety and Efficacy of Remote Ischemic Preconditioning in
11
12 Patients With Severe Carotid Artery Stenosis Before Carotid Artery Stenting: A Proof-of-
13
14 Concept, Randomized Controlled Trial. *Circulation* 2017;135(14):1325-35. doi:
15
16 10.1161/CIRCULATIONAHA.116.024807
17
- 18 27. Hougaard KD, Hjort N, Zeidler D, et al. Remote ischemic perconditioning as an adjunct
19
20 therapy to thrombolysis in patients with acute ischemic stroke: a randomized trial. *Stroke*
21
22 2014;45(1):159-67. doi: 10.1161/STROKEAHA.113.001346
23
- 24 28. England TJ, Hedstrom A, O'Sullivan S, et al. RECAST (Remote Ischemic Conditioning After
25
26 Stroke Trial): A Pilot Randomized Placebo Controlled Phase II Trial in Acute Ischemic
27
28 Stroke. *Stroke* 2017;48(5):1412-15. doi: 10.1161/STROKEAHA.116.016429
29
- 30 29. Koch S, Katsnelson M, Dong C, et al. Remote ischemic limb preconditioning after
31
32 subarachnoid hemorrhage: a phase Ib study of safety and feasibility. *Stroke*
33
34 2011;42(5):1387-91. doi: 10.1161/STROKEAHA.110.605840
35
- 36 30. Zhao W, Zhang J, Sadowsky MG, et al. Remote ischaemic conditioning for preventing and
37
38 treating ischaemic stroke. *Cochrane Database of Systematic Reviews* 2017(1)
39
40
- 41 31. Hildebrandt HA, Kreienkamp V, Gent S, et al. Kinetics and signal activation properties of
42
43 circulating factor(s) from healthy volunteers undergoing remote ischemic pre-
44
45 conditioning. *JACC Basic Transl Sci* 2016;1(1-2):3-13. doi: 10.1016/j.jacbts.2016.01.007
46
- 47 32. Pickard JM, Davidson SM, Hausenloy DJ, et al. Co-dependence of the neural and humoral
48
49 pathways in the mechanism of remote ischemic conditioning. *Basic Res Cardiol*
50
51 2016;111(4):50. doi: 10.1007/s00395-016-0568-z
52
53
54
55
56
57
58
59
60

- 1
2
3 33. Johnsen J, Pryds K, Salman R, et al. The remote ischemic preconditioning algorithm: effect
4 of number of cycles, cycle duration and effector organ mass on efficacy of protection.
5 *Basic Res Cardiol* 2016;111(2):10. doi: 10.1007/s00395-016-0529-6
6
7
8
9 34. Smith EE, Cieslak A, Barber P, et al. Therapeutic strategies and drug development for
10 vascular cognitive impairment. *J Am Heart Assoc* 2017;6(5):e005568. doi:
11 10.1161/JAHA.117.005568
12
13
14
15 35. Hansson L, Hedner T, Dahlof B. Prospective randomized open blinded end-point (PROBE)
16 study. A novel design for intervention trials. Prospective Randomized Open Blinded End-
17 Point. *Blood Press* 1992;1(2):113-9. [published Online First: 1992/08/01]
18
19
20
21 36. Nasreddine ZS, Phillips NA, Bedirian V, et al. The Montreal Cognitive Assessment, MoCA: a
22 brief screening tool for mild cognitive impairment. *Journal of the American Geriatrics*
23 *Society* 2005;53(4):695-9. doi: 10.1111/j.1532-5415.2005.53221.x [published Online
24 First: 2005/04/09]
25
26
27
28
29 37. Reitan RM. Validity of the Trail Making Test as an indicator of organic brain damage.
30 *Percept Motor Skills* 1958;8:271-76.
31
32
33 38. Rosen W. Verbal fluency in aging and dementia. *J Clin Neuropsychol* 1980;2:135-46.
34
35
36 39. Barr A, Brandt J. Word-list generation deficits in dementia. *J Clin Exp Neuropsychol*
37 1996;18(6):810-22.
38
39
40 40. Mirra SS, Heyman A, McKeel D, et al. The Consortium to Establish a Registry for
41 Alzheimer's Disease (CERAD). Part II. Standardization of the neuropathologic
42 assessment of Alzheimer's disease. *Neurology* 1991;41(4):479-86. [published Online
43 First: 1991/04/01]
44
45
46 41. Baykara E, Gesierich B, Adam R, et al. A novel imaging marker for small vessel disease
47 based on skeletonization of white matter tracts and diffusion histograms. *Annals of*
48 *neurology* 2016;80(4):581-92. doi: 10.1002/ana.24758
49
50
51
52
53
54
55
56
57
58
59

- 1
2
3 42. Shi Y, Thrippleton MJ, Makin SD, et al. Cerebral blood flow in small vessel disease: A
4
5 systematic review and meta-analysis. *Journal of cerebral blood flow and metabolism :
6
7 official journal of the International Society of Cerebral Blood Flow and Metabolism*
8
9 2016;36(10):1653-67. doi: 10.1177/0271678X16662891
10
- 11 43. Schuff N, Matsumoto S, Kmiecik J, et al. Cerebral blood flow in ischemic vascular dementia
12
13 and Alzheimer's disease, measured by arterial spin-labeling magnetic resonance
14
15 imaging. *Alzheimer's & dementia : the journal of the Alzheimer's Association*
16
17 2009;5(6):454-62. doi: 10.1016/j.jalz.2009.04.1233
18
19
- 20 44. Chen Y, Wang DJ, Detre JA. Test-retest reliability of arterial spin labeling with common
21
22 labeling strategies. *Journal of magnetic resonance imaging : JMRI* 2011;33(4):940-9.
23
24 doi: 10.1002/jmri.22345
25
- 26 45. Wu B, Lou X, Wu X, et al. Intra- and interscanner reliability and reproducibility of 3D whole-
27
28 brain pseudo-continuous arterial spin-labeling MR perfusion at 3T. *Journal of magnetic
29
30 resonance imaging : JMRI* 2014;39(2):402-9. doi: 10.1002/jmri.24175
31
32
- 33 46. Wahlund LO, Barkhof F, Fazekas F, et al. A new rating scale for age-related white matter
34
35 changes applicable to MRI and CT. *Stroke* 2001;32(6):1318-22.
36
- 37 47. Galvin JE, Roe CM, Powlishta KK, et al. The AD8: a brief informant interview to detect
38
39 dementia. *Neurology* 2005;65(4):559-64. doi: 10.1212/01.wnl.0000172958.95282.2a
40
- 41 48. Bucks RS, Ashworth DL, Wilcock GK, et al. Assessment of activities of daily living in
42
43 dementia: development of the Bristol Activities of Daily Living Scale. *Age and ageing*
44
45 1996;25(2):113-20.
46
- 47 49. Ismail Z, Aguera-Ortiz L, Brodaty H, et al. The Mild Behavioral Impairment Checklist (MBI-
48
49 C): A Rating Scale for Neuropsychiatric Symptoms in Pre-Dementia Populations. *Journal
50
51 of Alzheimer's disease : JAD* 2017;56(3):929-38. doi: 10.3233/JAD-160979
52
53
54
55
56
57
58
59
60

1
2
3 50. Ismail Z, Aguera-Ortiz L, Brodaty H, et al. The Mild Behavioral Impairment Checklist (MBI-
4
5 C): A rating scale for neuropsychiatric symptoms in pre-dementia populations. *Journal of*
6
7 *Alzheimer's disease : JAD* 2017;56(3):929-38. doi: 10.3233/JAD-160979
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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: 1. Beginning confluent WMH (ARWMC ⁴⁶ grade 2) on any slice on CT or MRI OR 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 $<100 \times 10^9/L$, 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

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| 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.

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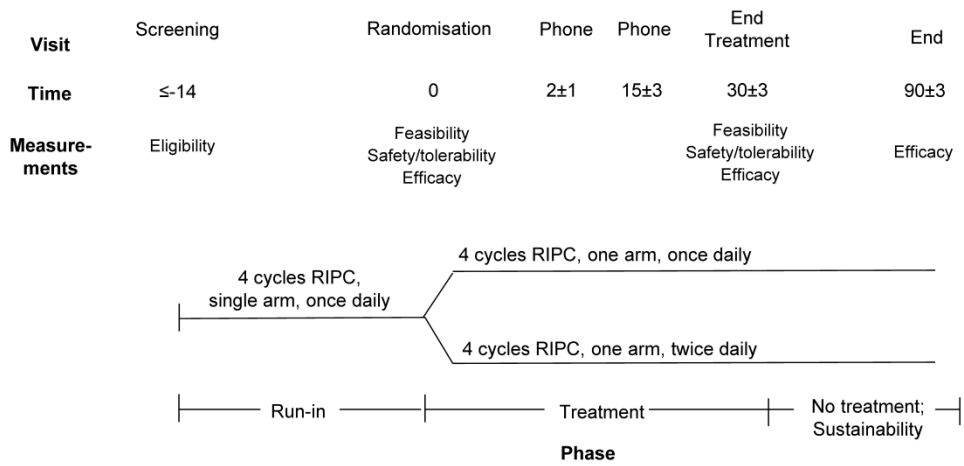


Figure 1. Trial design for the TRIC-VCI study.

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)

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3 **SUPPLEMENTARY FILE 1: HOW OUTCOME MEASURES WILL BE MEASURED**
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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: 1. Patient declares unwillingness to proceed with the intervention, OR 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.psm-d-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 encephalomalacia 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: <ol style="list-style-type: none"> 1. Mean change in total MoCA scores. 2. Proportion with decline in total MoCA ≥ 2 points. 3. Mean change in MoCA visuospatial/executive subscore. 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: <ol style="list-style-type: none"> 1. Homocysteine 2. Circulating nitrite 3. Interleukin-10 4. Matrix metalloproteinase 2 and 9 5. TNF-alpha 6. Interferon gamma 7. MicroRNA-144 8. SDF-1-alpha 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 Score⁵⁰.
- Cognitive performance, using the MoCA.
- Informant reports of cognitive decline and functional status using BADLS, AD8, and IQCODE short form⁵¹ 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 $\geq 80\%$ 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 $\geq 80\%$ 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 $\geq 80\%$ 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
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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 Radiology⁵⁸, 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	<i>b</i> =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.

Peer review only

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.

Ethics ID: REB19-0861

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

PI: Dr. Eric E. Smith

Version 4.0

Date: January 7, 2020 peer review only - <http://bmjopen.bmj.com/site/about/guidelines.xhtml> Page 1 of 12

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.

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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).

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- 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

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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 **do not** 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

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- 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.

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Potential Interactions with Other Medications: You can continue to take all your 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.

1 The investigators can remove you from the study at any time, even if you want to stay in the study.

2 This could happen if:

- 3
- 4 • The study investigator believes it is best for you to stop being in the study
 - 5 • You do not follow the study directions
 - 6 • The sponsor stops funding the study for any reason
- 7

8 You can stop participating at any time. However, if you decide to stop participating in the study,
9 we encourage you to talk to the study team. To help you leave the study safely, the study doctor
10 may ask you to complete some tests. Your decision will be honored and will be discussed with
11 your Substitute Decision Maker (SDM).
12

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

14 You will not be compensated for your participation in this study. However, you and your caregiver
15 will be reimbursed for parking expenses for each study visit.
16

17 There is no cost to you for the study visits or tests that are part of the study. In addition, you do
18 not have to pay for RIC study device – it will be provided to you for the duration of the study. At
19 the end of the study, you will be asked to return the device.
20

21 **WILL MY RECORDS BE KEPT PRIVATE?**

22 Any of your personal information (information about you and your health that identifies you as an
23 individual) collected or obtained, whether you choose to participate or not, will be kept confidential
24 and protected to the fullest extent of the law. All personal information collected will be kept in a
25 secure location. All computers used to hold information will be encrypted as per University of
26 Calgary policy. The data for this study will be retained for 25 years.
27

28 You have the right to have any information about you and your health that is collected, used or
29 disclosed for this study to be handled in a confidential manner.
30

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

- 35 • name,
- 36 • address
- 37 • telephone number,
- 38 • date of birth,
- 39 • new and existing medical records, or
- 40 • the types, dates and results of various tests and procedures.

41 You have the right to access, review and request changes to your personal health
42 information.
43

44 Access to your personal health information will take place under the supervision of the Principal
45 Investigator.
46

47 “Study data” is health information about you that is collected for the study, but that does not
48 directly identify you. Any study data about you that is sent outside of the hospital will have a code
49 and will not contain your name or address, or any information that directly identifies you.
50

51 Ethics ID: REB19-0861

52 Study Title: Trial of Remote Ischemic Pre-Conditioning in Vascular Cognitive Impairment

53 PI: Dr. Eric E. Smith

54 Version 4.0 For peer review only - <http://bmjopen.bmj.com/site/about/guidelines.xhtml>

55 Date: January 7, 2020

1 Your full date of birth will be included on all images (i.e. MRI scans) disclosed outside the
2 institution for the purpose of the study.
3

4
5 Study data that is sent outside of the hospital will be used for the research purposes explained in
6 this consent form. As part of a movement to more open science, researchers now share the
7 information collected in their studies with each other. This will include your study data, but not any
8 of your personal health information. The study data may be placed on websites such as the
9 University of Calgary PRISM Dataverse (<https://libanswers.ucalgary.ca/faq/164924>).
10

11
12 The investigator(s), study staff and the other people listed above will keep the information
13 they see or receive about you confidential, to the extent permitted by applicable laws. Even
14 though the risk of identifying you from the study data is very small, it can never be
15 completely eliminated.
16

17
18 The study staff, the Conjoint Health Research Ethics Board at the University of Calgary, the
19 monitor(s), and the regulatory authority (Health Canada) will have access to your personal
20 information for purposes associated with the study, but will only be allowed to access your records
21 under the supervision of the Principal Investigator and will be obligated to protect your privacy
22 and not disclose your personal information. None of your personal information will be given to
23 anyone without your permission unless required by law. When the results of this study are
24 published, your identity will not be disclosed. Even though the risk of identifying you from the study
25 data is very small, it can never be completely eliminated.
26

27 Authorized representatives from the University of Calgary and the Conjoint Health Research
28 Ethics Board may look at your identifiable medical/clinical study records held at the University of
29 Calgary for quality assurance purposes.
30

31 When the results of this study are published, your identity will not be disclosed.
32

33 You have the right to be informed of the results of this study once the entire study is complete.
34

35
36 A description of this clinical trial will be available on <http://www.ClinicalTrials.gov>, as required by
37 U.S. Law. This website will not include information that can identify you. At most, the website will
38 include a summary of the results of all participants. You can search this website at any time.
39

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

41
42 You may contact the individuals listed at the beginning of this consent form at any time for
43 treatment of side effects, questions, emergencies or FOR ANY OTHER REASON. In the event
44 that you suffer injury as a result of participating in this research, no compensation will be provided
45 to you by the University of Calgary, Alberta Health Services or the Researchers. Nonetheless,
46 you still have all your legal rights. Nothing said in this consent form alters your right to seek
47 damages.
48

49
50 All participants in a research study have the following rights:

- 51
52 1. You have the right to have this form and all information concerning this study explained to you
53 and if you wish translated into your preferred language.
54
55
56

57 Ethics ID: REB19-0861

58 Study Title: Trial of Remote Ischemic Pre-Conditioning in Vascular Cognitive Impairment

59 PI: Dr. Eric E. Smith

60 Version 4.0 For peer review only - <http://bmjopen.bmj.com/site/about/guidelines.xhtml>

Date: January 7, 2020

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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)
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Investigator Name	Signature	Date (DD/MMM/YY)
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Witness' Name	Signature	Date (DD/MMM/YY)
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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.

Ethics ID: REB19-0861

Study Title: Trial of Remote Ischemic Pre-Conditioning in Vascular Cognitive Impairment

PI: Dr. Eric E. Smith

Version 4.0 For peer review only - <http://bmjopen.bmj.com/site/about/guidelines.xhtml>

Date: January 7, 2020

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.

Ethics ID: REB19-0861

Study Title: Trial of Remote Ischemic Pre-Conditioning in Vascular Cognitive Impairment

PI: Dr. Eric E. Smith

Version 4.0 For peer review only - <http://bmjopen.bmj.com/site/about/guidelines.xhtml>

Date: January 7, 2020

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CRU #044 TRIC VCI

Plate #001

Screening

Subject ID:

Centre

Subject ID

Date:

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SCREENING (page 1 of 6)

Has the research candidate and their study partner given informed consent and signed the consent forms?	<input type="checkbox"/> Yes	<input type="checkbox"/> No
---	------------------------------	-----------------------------

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



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)	<input type="checkbox"/> Yes	<input type="checkbox"/> No
Neuroimaging evidence of mass lesion, intracerebral hemorrhage, vascular malformation, or evidence non-vascular disease such as hydrocephalus	<input type="checkbox"/> Yes	<input type="checkbox"/> No
Resides in a long term care facility	<input type="checkbox"/> Yes	<input type="checkbox"/> No
Other significant neurological or psychiatric disease (e.g. multiple sclerosis)	<input type="checkbox"/> Yes	<input type="checkbox"/> No
Subject does not have a study partner who can provide corroborative information	<input type="checkbox"/> Yes	<input type="checkbox"/> No
English or French is not sufficiently proficient for clinical assessment and neuropsychological testing	<input type="checkbox"/> Yes	<input type="checkbox"/> No
Total score on the MoCA 12 or lower	<input type="checkbox"/> Yes	<input type="checkbox"/> No
Unable to undergo MRI due to medical contraindications such a cardiac pacemaker, or inability to tolerate the procedure	<input type="checkbox"/> Yes	<input type="checkbox"/> 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	<input type="checkbox"/> Yes	<input type="checkbox"/> No
On therapeutic anticoagulation with doses used for treatment of deep venous thrombosis, pulmonary embolism, or for stroke prevention in atrial fibrillation	<input type="checkbox"/> Yes	<input type="checkbox"/> No
Significant bleeding diathesis	<input type="checkbox"/> Yes	<input type="checkbox"/> No
Any symptomatic or previously known arm soft-tissue disease, vascular injury, or peripheral vascular disease (PVD)	<input type="checkbox"/> Yes	<input type="checkbox"/> No
Hypertension with systolic blood pressure >=180 mmHg despite medical treatment at the time of enrolment	<input type="checkbox"/> Yes	<input type="checkbox"/> No
Planned revascularization (any angioplasty or vascular surgery) within the next 3 months	<input type="checkbox"/> Yes	<input type="checkbox"/> No
Planned surgical procedure within the next 3 months	<input type="checkbox"/> Yes	<input type="checkbox"/> No
Currently receiving an investigational drug or device by other studies	<input type="checkbox"/> Yes	<input type="checkbox"/> No

Signature of investigator confirms the Inclusion/Exclusion Criteria : _____

e-signature
iDataFax use only

:

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PI's printed first and last name: _____



CRU #044 TRIC VCI

Plate #003

Screening

Subject ID:

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Centre

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Subject ID

Date:

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SCREENING (page 3 of 6)

DEMOGRAPHICS

1. Age:	<table border="1" style="width: 100%; height: 20px;"> <tr> <td style="width: 20px;"></td> <td style="width: 20px;"></td> </tr> </table>		
2. Sex:	<input type="checkbox"/> Male <input type="checkbox"/> Female		
3. Mother tongue (first language learned):	<input type="checkbox"/> English <input type="checkbox"/> French <input type="checkbox"/> Other: _____		
4. Marital Status:	<input type="checkbox"/> Single <input type="checkbox"/> Separated <input type="checkbox"/> Married <input type="checkbox"/> Divorced <input type="checkbox"/> Common-law partnership <input type="checkbox"/> Widowed		
5. Current living circumstance:	<input type="checkbox"/> House or apartment/condominium that you own <input type="checkbox"/> Apartment/condominium or house that you rent <input type="checkbox"/> Retirement home (autonomous living) <input type="checkbox"/> Residence for semi-autonomous individuals <input type="checkbox"/> Nursing home or long-term care (assisted living) <input type="checkbox"/> Other, please specify: _____		
6. What is the highest grade or level of school completed or highest degree obtained:	<table style="width: 100%;"> <tr> <td style="width: 50%; vertical-align: top;"> <input type="checkbox"/> Never attended school <input type="checkbox"/> Some primary/grade school <input type="checkbox"/> Completed primary/grade school <input type="checkbox"/> Some high school <input type="checkbox"/> Completed high school <input type="checkbox"/> Apprenticeship </td> <td style="width: 50%; vertical-align: top;"> <input type="checkbox"/> Technical school or community college <input type="checkbox"/> CEGEP <input type="checkbox"/> Undergraduate degree at university (e.g., B.A, B.SC, B.Eng., LL.B., B.Ed., etc) <input type="checkbox"/> Some graduate (post-undergraduate) school <input type="checkbox"/> Graduate degree at university </td> </tr> </table>	<input type="checkbox"/> Never attended school <input type="checkbox"/> Some primary/grade school <input type="checkbox"/> Completed primary/grade school <input type="checkbox"/> Some high school <input type="checkbox"/> Completed high school <input type="checkbox"/> Apprenticeship	<input type="checkbox"/> Technical school or community college <input type="checkbox"/> CEGEP <input type="checkbox"/> Undergraduate degree at university (e.g., B.A, B.SC, B.Eng., LL.B., B.Ed., etc) <input type="checkbox"/> Some graduate (post-undergraduate) school <input type="checkbox"/> Graduate degree at university
<input type="checkbox"/> Never attended school <input type="checkbox"/> Some primary/grade school <input type="checkbox"/> Completed primary/grade school <input type="checkbox"/> Some high school <input type="checkbox"/> Completed high school <input type="checkbox"/> Apprenticeship	<input type="checkbox"/> Technical school or community college <input type="checkbox"/> CEGEP <input type="checkbox"/> Undergraduate degree at university (e.g., B.A, B.SC, B.Eng., LL.B., B.Ed., etc) <input type="checkbox"/> Some graduate (post-undergraduate) school <input type="checkbox"/> Graduate degree at university		

CRU #044 TRIC VCI

Plate #004

Screening

Subject ID:

Centre

Subject ID

Date:

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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:

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Centre

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Subject ID

Date:

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SCREENING (page 5 of 6)

MEDICAL HISTORY							
1. History of prior transient ischemic attack:	<input type="checkbox"/> Yes <input type="checkbox"/> No						
If yes, then complete 1.a. and 1.b.							
1.a. Is there a history of more than one prior transient ischemic attack?	<input type="checkbox"/> Yes <input type="checkbox"/> No						
1.b. What was the month and year of the most recent prior transient attack?	<table border="1" style="display: inline-table; margin-right: 20px;"> <tr> <td style="width: 20px; height: 20px;"></td> <td style="width: 20px; height: 20px;"></td> <td style="width: 20px; height: 20px;"></td> <td style="width: 20px; height: 20px;"></td> </tr> </table> <table border="1" style="display: inline-table;"> <tr> <td style="width: 20px; height: 20px;"></td> <td style="width: 20px; height: 20px;"></td> </tr> </table> <p style="text-align: center; margin-top: 5px;">y y y y m m</p>						
2. History of prior stroke:	<input type="checkbox"/> Yes <input type="checkbox"/> No						
If yes, then complete 2.a and 2.b.							
2.a. Is there a history of more than one prior stroke?	<input type="checkbox"/> Yes <input type="checkbox"/> No						
2.b. What was the month and year of the most recent prior stroke?	<table border="1" style="display: inline-table; margin-right: 20px;"> <tr> <td style="width: 20px; height: 20px;"></td> <td style="width: 20px; height: 20px;"></td> <td style="width: 20px; height: 20px;"></td> <td style="width: 20px; height: 20px;"></td> </tr> </table> <table border="1" style="display: inline-table;"> <tr> <td style="width: 20px; height: 20px;"></td> <td style="width: 20px; height: 20px;"></td> </tr> </table> <p style="text-align: center; margin-top: 5px;">y y y y m m</p>						
3. History of carotid stenosis:	<input type="checkbox"/> Yes <input type="checkbox"/> No						
4. History of prior carotid revascularization:	<input type="checkbox"/> Yes <input type="checkbox"/> No						
4.a. Side of carotid revascularization:	<input type="checkbox"/> R <input type="checkbox"/> L <input type="checkbox"/> Both						
5. History of hypertension or use of antihypertensive medications to control blood pressure:	<input type="checkbox"/> Yes <input type="checkbox"/> No						
6. History of diabetes mellitus:	<input type="checkbox"/> Yes <input type="checkbox"/> No						
7. History of dyslipidemia or use of antilipid medications:	<input type="checkbox"/> Yes <input type="checkbox"/> No						
8. History of myocardial infarction:	<input type="checkbox"/> Yes <input type="checkbox"/> No						
9. History of angina:	<input type="checkbox"/> Yes <input type="checkbox"/> No						
10. History of atrial fibrillation:	<input type="checkbox"/> Yes <input type="checkbox"/> No						
11. History of heart failure:	<input type="checkbox"/> Yes <input type="checkbox"/> No						



CRU #044 TRIC VCI

Plate #006

Screening

Subject ID:

Centre

Subject ID

Date:

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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?		<input type="checkbox"/> Yes	<input type="checkbox"/> No
If yes, please answer 1.a. below:			
1.a. Antiplatelet drug class(es)—select all that apply:			
<input type="checkbox"/> Acetylsalicylic acid (e.g. Aspirin)	<input type="checkbox"/> Persantine		
<input type="checkbox"/> Clopidogrel (Plavix)	<input type="checkbox"/> Ticagrelor (Brilinta)		
<input type="checkbox"/> Aggrenox	<input type="checkbox"/> Prasugrel (Effient)		
2. Is the patient taking an anticoagulant drug?		<input type="checkbox"/> Yes	<input type="checkbox"/> 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?		<input type="checkbox"/> Yes	<input type="checkbox"/> 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:

<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>
Centre		Subject ID	

Date:

<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>
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	<input type="checkbox"/> Yes	<input type="checkbox"/> No	<input type="checkbox"/> Yes	<input type="checkbox"/> No
Ulnar pulse palpable	<input type="checkbox"/> Yes	<input type="checkbox"/> No	<input type="checkbox"/> Yes	<input type="checkbox"/> No
Brachial pulse palpable	<input type="checkbox"/> Yes	<input type="checkbox"/> No	<input type="checkbox"/> Yes	<input type="checkbox"/> No
Local edema	<input type="checkbox"/> Yes	<input type="checkbox"/> No	<input type="checkbox"/> Yes	<input type="checkbox"/> No
Skin breakdown	<input type="checkbox"/> Yes	<input type="checkbox"/> No	<input type="checkbox"/> Yes	<input type="checkbox"/> No
Rash	<input type="checkbox"/> Yes	<input type="checkbox"/> No	<input type="checkbox"/> Yes	<input type="checkbox"/> No
Petechiae	<input type="checkbox"/> Yes	<input type="checkbox"/> No	<input type="checkbox"/> Yes	<input type="checkbox"/> No
Upper arm tenderness	<input type="checkbox"/> Yes	<input type="checkbox"/> No	<input type="checkbox"/> Yes	<input type="checkbox"/> No
Lower arm tenderness	<input type="checkbox"/> Yes	<input type="checkbox"/> No	<input type="checkbox"/> Yes	<input type="checkbox"/> No

3. Arm examination comments:

4. Examiner blinded to treatment arm:

 Yes
 No

Signature: _____

Date:

<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>
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	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>	0 - Alert 1 - Not alert, but arousable with minimal stimulation 2 - Not alert, requires repeated stimulation to attend 3 - Coma
1b. LOC Questions <i>Ask patient the month and their age</i>	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>	0 - Answers both correctly 1 - Answers one correctly 2 - Both incorrect
1c. LOC Commands <i>Ask patient to open/close eyes and form/release fist</i>	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>	0 - Obeys both correctly 1 - Obeys one correctly 2 - Both incorrect
2. Best Gaze <i>Only horizontal eye movement</i>	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>	0 - Normal 1 - Partial gaze palsy 2 - Forced gaze palsy
3. Visual Field Testing	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>	0 - No visual field loss 1 - Partial hemianopia 2 - Complete hemianopia 3 - Bilateral hemianopia (blind, incl. Cortical blindness)
4. Facial Palsy <i>Ask patient to show teeth or raise eyebrows and close eyes tightly</i>	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>	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:

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NIH STROKE SCALE (page 2 of 3)

	L	R	
5. Motor Function Arm	<input type="checkbox"/>	<input type="checkbox"/>	0 - Normal (extends arm 90° or 45° for 10 sec without drift)
	<input type="checkbox"/>	<input type="checkbox"/>	1 - Drift
	<input type="checkbox"/>	<input type="checkbox"/>	2 - Some effort against gravity
	<input type="checkbox"/>	<input type="checkbox"/>	3 - No effort against gravity
	<input type="checkbox"/>	<input type="checkbox"/>	4 - No movement
	<input type="checkbox"/>	<input type="checkbox"/>	9 - Untestable (Joint fused/limb amputated) (<i>do not add score</i>)
6. Motor Function Leg	<input type="checkbox"/>	<input type="checkbox"/>	0 - Normal (holds leg in 30° position for 5 sec without drift)
	<input type="checkbox"/>	<input type="checkbox"/>	1 - Drift
	<input type="checkbox"/>	<input type="checkbox"/>	2 - Some effort against gravity
	<input type="checkbox"/>	<input type="checkbox"/>	3 - No effort against gravity
	<input type="checkbox"/>	<input type="checkbox"/>	4 - No movement
	<input type="checkbox"/>	<input type="checkbox"/>	9 - Untestable (Joint fused/limb amputated) (<i>do not add score</i>)
7. Limb ataxia	<input type="checkbox"/>		0 - No ataxia
	<input type="checkbox"/>		1 - Present in one limb
	<input type="checkbox"/>		2 - Present in two limbs
8. Sensory <i>Use pinprick to test arms, legs, trunk and face, compare side to side</i>	<input type="checkbox"/>		0 - Normal
	<input type="checkbox"/>		1 - Mild to moderate decrease in sensation
	<input type="checkbox"/>		2 - Severe to total sensory loss
9. Best Language <i>Ask patient to describe picture, name items</i>	<input type="checkbox"/>		0 - No aphasia
	<input type="checkbox"/>		1 - Mild to moderate aphasia
	<input type="checkbox"/>		2 - Severe aphasia
	<input type="checkbox"/>		3 - Mute



CRU #044 TRIC VCI

Plate #012

Screening

Subject ID:

Centre

Subject ID

Date:

yyyy

mm

dd

HACHINSKI ISCHEMIC SCORE

Characteristic	YES	NO
Abrupt onset	<input type="checkbox"/> ₂	<input type="checkbox"/> ₀
Stepwise deterioration	<input type="checkbox"/> ₁	<input type="checkbox"/> ₀
Fluctuating course	<input type="checkbox"/> ₂	<input type="checkbox"/> ₀
Nocturnal confusion	<input type="checkbox"/> ₁	<input type="checkbox"/> ₀
Preservation of personality	<input type="checkbox"/> ₁	<input type="checkbox"/> ₀
Depression	<input type="checkbox"/> ₁	<input type="checkbox"/> ₀
Somatic complaints	<input type="checkbox"/> ₁	<input type="checkbox"/> ₀
Emotional lability	<input type="checkbox"/> ₁	<input type="checkbox"/> ₀
History of hypertension	<input type="checkbox"/> ₁	<input type="checkbox"/> ₀
History of stroke	<input type="checkbox"/> ₂	<input type="checkbox"/> ₀
Associated atherosclerosis	<input type="checkbox"/> ₁	<input type="checkbox"/> ₀
Focal neurological symptoms	<input type="checkbox"/> ₂	<input type="checkbox"/> ₀
Focal neurological signs	<input type="checkbox"/> ₂	<input type="checkbox"/> 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)

<p>VISUOSPATIAL / EXECUTIVE</p>		<p>Draw CLOCK (Ten past eleven) (3 points)</p> <p><input type="checkbox"/> Contour <input type="checkbox"/> Numbers <input type="checkbox"/> Hands</p>	<p>POINTS</p> <p><input type="text"/> /5</p>																		
<p>NAMING</p>			<p><input type="text"/> /3</p>																		
<p>MEMORY</p> <p>Read list of words, subject must repeat them. Do 2 trials. Do a recall after 5 minutes.</p>	<table border="1"> <tr> <td></td> <td>FACE</td> <td>VELVET</td> <td>CHURCH</td> <td>DAISY</td> <td>RED</td> </tr> <tr> <td>1st trial</td> <td><input type="checkbox"/></td> <td><input type="checkbox"/></td> <td><input type="checkbox"/></td> <td><input type="checkbox"/></td> <td><input type="checkbox"/></td> </tr> <tr> <td>2nd trial</td> <td><input type="checkbox"/></td> <td><input type="checkbox"/></td> <td><input type="checkbox"/></td> <td><input type="checkbox"/></td> <td><input type="checkbox"/></td> </tr> </table>		FACE	VELVET	CHURCH	DAISY	RED	1st trial	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	2nd trial	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>		<p>No Points</p>
	FACE	VELVET	CHURCH	DAISY	RED																
1st trial	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>																
2nd trial	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>																
<p>ATTENTION</p> <p>Read list of digits (1 digit/sec).</p> <p>Subject has to repeat them in the forward order <input type="checkbox"/> 2 1 8 5 4</p> <p>Subject has to repeat them in the backward order <input type="checkbox"/> 7 4 2</p>			<p><input type="text"/> /2</p>																		
<p>Read list of letters. The subject must tap with his hand at each letter A. No points if ≥ 2 errors</p> <p><input type="checkbox"/> 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</p>			<p><input type="text"/> /1</p>																		
<p>Serial 7 subtraction starting at 100</p> <p><input type="checkbox"/> 93 <input type="checkbox"/> 86 <input type="checkbox"/> 79 <input type="checkbox"/> 72 <input type="checkbox"/> 65</p> <p>4 or 5 correct subtractions: 3 pts, 2 or 3 correct: 2 pts, 1 correct: 1 pt, 0 correct: 0 pt</p>			<p><input type="text"/> /3</p>																		



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

<table border="1" style="border-collapse: collapse; width: 100%;"> <tr> <td style="width: 25px; height: 25px;"></td> <td style="width: 25px; height: 25px;"></td> </tr> </table> <p style="text-align: center; margin: 0;">Centre</p>			<table border="1" style="border-collapse: collapse; width: 100%;"> <tr> <td style="width: 25px; height: 25px;"></td> <td style="width: 25px; height: 25px;"></td> <td style="width: 25px; height: 25px;"></td> </tr> </table> <p style="text-align: center; margin: 0;">Subject ID</p>			

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



CRU #044 TRIC VCI

Plate #016

 Screening Randomization
 Follow Up End

Subject ID:

Centre

Subject ID

Date:

y y y y

m m

d d

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

4. DRINKING	<input type="checkbox"/>	a) Drinks appropriately
	<input type="checkbox"/>	b) Drinks appropriately with aids, beaker/straw etc.
	<input type="checkbox"/>	c) Does not drink appropriately even with aids but attempts to
	<input type="checkbox"/>	d) Has to have drinks administered (fed)
	<input type="checkbox"/>	e) Not applicable
5. DRESSING	<input type="checkbox"/>	a) Selects appropriate clothing and dresses self
	<input type="checkbox"/>	b) Puts clothes on in wrong order and/or back to front and/or dirty clothing
	<input type="checkbox"/>	c) Unable to dress self but moves limbs to assist
	<input type="checkbox"/>	d) Unable to assist and requires total dressing
	<input type="checkbox"/>	e) Not applicable
6. HYGIENE	<input type="checkbox"/>	a) Washes regularly and independently
	<input type="checkbox"/>	b) Can wash self if given soap, flannel, towel, etc.
	<input type="checkbox"/>	c) Can wash self if prompted and supervised
	<input type="checkbox"/>	d) Unable to wash self and needs full assistance
	<input type="checkbox"/>	e) Not applicable
7. TEETH	<input type="checkbox"/>	a) Cleans own teeth/dentures regularly and independently
	<input type="checkbox"/>	b) Cleans teeth/dentures if given appropriate items
	<input type="checkbox"/>	c) Requires some assistance, toothpaste on brush, brush to mouth etc.
	<input type="checkbox"/>	d) Full assistance given
	<input type="checkbox"/>	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	<input type="checkbox"/> a) Bathes regularly and independently <input type="checkbox"/> b) Needs bath to be drawn/shower turned on but washes independently <input type="checkbox"/> c) Needs supervision and prompting to wash <input type="checkbox"/> d) Totally dependent, needs full assistance <input type="checkbox"/> e) Not applicable
9. TOILET/COMMODE	<input type="checkbox"/> a) Uses toilet appropriately when required <input type="checkbox"/> b) Needs to be taken to the toilet and given assistance <input type="checkbox"/> c) Incontinent of urine or faeces <input type="checkbox"/> d) Incontinent of urine and faeces <input type="checkbox"/> e) Not applicable
10. TRANSFERS	<input type="checkbox"/> a) Can get in/out of chair unaided <input type="checkbox"/> b) Can get into a chair but needs help to get out <input type="checkbox"/> c) Needs help getting in and out of a chair <input type="checkbox"/> d) Totally dependent on being put into and lifted from chair <input type="checkbox"/> e) Not applicable
11. MOBILITY	<input type="checkbox"/> a) Walks independently <input type="checkbox"/> b) Walks with assistance i.e. furniture, arm for support <input type="checkbox"/> c) Uses aids to mobilise i.e. frame, sticks etc. <input type="checkbox"/> d) Unable to walk <input type="checkbox"/> e) Not applicable



CRU #044 TRIC VCI

Plate #018

 Screening
 Randomization

 Follow Up
 End

Subject ID:

Centre

Subject ID

Date:

y y y y

m m

d d

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

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



CRU #044 TRIC VCI

Plate #019

- Screening
- Randomization
- Follow Up
- End

Subject ID:

<i>Centre</i>		<i>Subject ID</i>	

Date:

<i>y y y y</i>				<i>m m</i>		<i>d d</i>	

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

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



CRU #044 TRIC VCI

Plate #020

 Screening
 Randomization

 Follow Up
 End

Subject ID:

Centre

Subject ID

Date:

y y y y

m m

d d

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

19. GAMES/HOBBIES	<input type="checkbox"/>	a) Participates in pastimes/activities to previous standard
	<input type="checkbox"/>	b) Participates but needs instruction/supervision
	<input type="checkbox"/>	c) Reluctant to join in, very slow needs coaxing
	<input type="checkbox"/>	d) No longer able or willing to join in
	<input type="checkbox"/>	e) Not applicable
20. TRANSPORT	<input type="checkbox"/>	a) Able to drive, cycle or use public transport independently
	<input type="checkbox"/>	b) Unable to drive but uses public transport or bike etc.
	<input type="checkbox"/>	c) Unable to use public transport alone
	<input type="checkbox"/>	d) Unable/unwilling to use transport even when accompanied
	<input type="checkbox"/>	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)	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
2. Less interest in hobbies/activities	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
3. Repeats the same things over and over (questions, stories, or statements)	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
4. Trouble learning how to use a tool, appliance, or gadget (e.g., VCR, computer, microwave, remote control)	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
5. Forgets correct month or year	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
6. Trouble handling complicated financial affairs (e.g., balancing checkbook, income taxes, paying bills)	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
7. Trouble remembering appointments	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
8. Daily problems with thinking and/or memory	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
		Total Score [0-8]	<input type="text"/>



CRU #044 TRIC VCI

Plate #022

Screening

Subject ID:

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Centre

Subject ID

Date:

--	--	--	--	--	--	--

yyyy

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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	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
2. Remembering things that have happened recently	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
3. Recalling conversations a few days later	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
4. Remembering his/her address and telephone number	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
5. Remembering what day and month it is	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
6. Remembering where things are usually kept	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
7. Remembering where to find things which have been put in a different place from usual	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
8. Knowing how to work familiar machines around the house	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
9. Learning to use a new gadget or machine around the house	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
10. Learning new things in general	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
11. Following a story in a book or on TV	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
12. Making decisions on everyday matters	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>



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	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
14. Handling financial matters e.g. the pension, dealing with the bank	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
15. Handling other everyday arithmetic problems e.g. knowing how much food to buy, knowing how long between visits from family or friends	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
16. Using his/her intelligence to understand what's going on and to reason things through	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>



CRU #044 TRIC VCI

Plate #024

 Randomization End

 Follow Up

Subject ID:

<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>
Centre		Subject ID		

Date:

<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>
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		
<i>This domain describes interest, motivation, and drive</i>					
Uninterested in friends, family, or home activities.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3
Lacking curiosity in topics that would usually have attracted interest.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3
Being less spontaneous and active – for example, less likely to initiate or maintain conversation.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3
Unmotivated to act on obligations or interests.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3
Lacking in affection or emotions when compared to usual self.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3
No longer caring about anything.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3
<i>This domain describes mood or anxiety symptoms</i>					
Sadness or being in low spirits. Episodes of tearfulness.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3
Less able to experience pleasure.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3
Feeling discouraged about the future or feeling like a failure.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3
Viewing self as a burden to family and friends.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3
Being more anxious or worried about things that are routine (e.g. events, visits, etc.).	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3
Feeling very tense, having an inability to relax, or having shakiness, or symptoms of panic.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 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
<i>This domain describes the ability to delay gratification and control behavior, impulses, oral intake and/or changes in reward</i>			
Agitation, aggression, irritability, or being temperamental.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/> 1 <input type="checkbox"/> 2 <input type="checkbox"/> 3
Being unreasonably or uncharacteristically argumentative.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/> 1 <input type="checkbox"/> 2 <input type="checkbox"/> 3
Impulsivity. Seeming to act without considering things.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/> 1 <input type="checkbox"/> 2 <input type="checkbox"/> 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.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/> 1 <input type="checkbox"/> 2 <input type="checkbox"/> 3
Frustration or impatience. Having troubles coping with delays, or waiting for events or for one's turn?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/> 1 <input type="checkbox"/> 2 <input type="checkbox"/> 3
Recklessness or lack of judgement when driving (e.g. speeding, erratic swerving, abrupt lane changes, etc.).	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/> 1 <input type="checkbox"/> 2 <input type="checkbox"/> 3
Stubbornness or rigidity, i.e., uncharacteristically insistent on having one's own way, or being unwilling/unable to see/hear other views.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/> 1 <input type="checkbox"/> 2 <input type="checkbox"/> 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).	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/> 1 <input type="checkbox"/> 2 <input type="checkbox"/> 3
Not finding food tasteful or enjoyable. Eating less.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/> 1 <input type="checkbox"/> 2 <input type="checkbox"/> 3
Hoarding objects.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/> 1 <input type="checkbox"/> 2 <input type="checkbox"/> 3
Simple repetitive behaviors or compulsions.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/> 1 <input type="checkbox"/> 2 <input type="checkbox"/> 3
Trouble regulating smoking, alcohol, drug intake, gambling, or shoplifting.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/> 1 <input type="checkbox"/> 2 <input type="checkbox"/> 3
<i>This domain describes following societal norms and having social graces, tact, and empathy</i>			
Unconcerned about how one's words or actions affect others. Insensitivity to others' feelings.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/> 1 <input type="checkbox"/> 2 <input type="checkbox"/> 3
Talking openly about very personal or private matters not usually discussed in public.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/> 1 <input type="checkbox"/> 2 <input type="checkbox"/> 3
Saying rude or crude things or making lewd sexual remarks.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/> 1 <input type="checkbox"/> 2 <input type="checkbox"/> 3
Lacking the social judgement about what to say or how to behave in public or private.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/> 1 <input type="checkbox"/> 2 <input type="checkbox"/> 3
Talking to strangers as if familiar, or intruding on their activities.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/> 1 <input type="checkbox"/> 2 <input type="checkbox"/> 3



CRU #044 TRIC VCI

Plate #026

Randomization End

Follow Up

Subject ID:

Centre

Subject ID

Date:

y y y y

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INFORMANT MBI TRACKING TOOL (page 3 of 3)

	YES	NO	SEVERITY
<i>This domain describes strongly held beliefs and sensory experiences</i>			
Having beliefs that one is in danger, or that others are planning harm or to steal one's belongings.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/> 1 <input type="checkbox"/> 2 <input type="checkbox"/> 3
Suspiciousness about the intentions or motives of other people.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/> 1 <input type="checkbox"/> 2 <input type="checkbox"/> 3
Unrealistic beliefs about one's power, wealth or skills.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/> 1 <input type="checkbox"/> 2 <input type="checkbox"/> 3
Hearing voices or talking to imaginary people or "spirits".	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/> 1 <input type="checkbox"/> 2 <input type="checkbox"/> 3
Seeing things (e.g. people, animals or insects) that are not there, i.e., that are imaginary to others?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/> 1 <input type="checkbox"/> 2 <input type="checkbox"/> 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	----	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/>	<input type="checkbox"/> 0 <input type="checkbox"/> 1 <input type="checkbox"/> 2 <input type="checkbox"/> 3 <input type="checkbox"/> 4 <input type="checkbox"/> 5 <input type="checkbox"/> 6 <input type="checkbox"/> 7 <input type="checkbox"/> 8 <input type="checkbox"/> 9 <input type="checkbox"/> 10
2	----	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/>	<input type="checkbox"/> 0 <input type="checkbox"/> 1 <input type="checkbox"/> 2 <input type="checkbox"/> 3 <input type="checkbox"/> 4 <input type="checkbox"/> 5 <input type="checkbox"/> 6 <input type="checkbox"/> 7 <input type="checkbox"/> 8 <input type="checkbox"/> 9 <input type="checkbox"/> 10
3	----	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/>	<input type="checkbox"/> 0 <input type="checkbox"/> 1 <input type="checkbox"/> 2 <input type="checkbox"/> 3 <input type="checkbox"/> 4 <input type="checkbox"/> 5 <input type="checkbox"/> 6 <input type="checkbox"/> 7 <input type="checkbox"/> 8 <input type="checkbox"/> 9 <input type="checkbox"/> 10
4	----	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/>	<input type="checkbox"/> 0 <input type="checkbox"/> 1 <input type="checkbox"/> 2 <input type="checkbox"/> 3 <input type="checkbox"/> 4 <input type="checkbox"/> 5 <input type="checkbox"/> 6 <input type="checkbox"/> 7 <input type="checkbox"/> 8 <input type="checkbox"/> 9 <input type="checkbox"/> 10
5	----	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/>	<input type="checkbox"/> 0 <input type="checkbox"/> 1 <input type="checkbox"/> 2 <input type="checkbox"/> 3 <input type="checkbox"/> 4 <input type="checkbox"/> 5 <input type="checkbox"/> 6 <input type="checkbox"/> 7 <input type="checkbox"/> 8 <input type="checkbox"/> 9 <input type="checkbox"/> 10
6	----	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/>	<input type="checkbox"/> 0 <input type="checkbox"/> 1 <input type="checkbox"/> 2 <input type="checkbox"/> 3 <input type="checkbox"/> 4 <input type="checkbox"/> 5 <input type="checkbox"/> 6 <input type="checkbox"/> 7 <input type="checkbox"/> 8 <input type="checkbox"/> 9 <input type="checkbox"/> 10
7	----	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/>	<input type="checkbox"/> 0 <input type="checkbox"/> 1 <input type="checkbox"/> 2 <input type="checkbox"/> 3 <input type="checkbox"/> 4 <input type="checkbox"/> 5 <input type="checkbox"/> 6 <input type="checkbox"/> 7 <input type="checkbox"/> 8 <input type="checkbox"/> 9 <input type="checkbox"/> 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	----	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/>	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> 0 1 2 3 4 5 <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> 6 7 8 9 10
2	----	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/>	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> 0 1 2 3 4 5 <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> 6 7 8 9 10
3	----	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/>	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> 0 1 2 3 4 5 <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> 6 7 8 9 10
4	----	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/>	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> 0 1 2 3 4 5 <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> 6 7 8 9 10
5	----	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/>	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> 0 1 2 3 4 5 <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> 6 7 8 9 10
6	----	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/>	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> 0 1 2 3 4 5 <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> 6 7 8 9 10
7	----	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/>	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> 0 1 2 3 4 5 <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> 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	----	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/>	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> 0 1 2 3 4 5 <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> 6 7 8 9 10
2	----	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/>	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> 0 1 2 3 4 5 <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> 6 7 8 9 10
3	----	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/>	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> 0 1 2 3 4 5 <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> 6 7 8 9 10
4	----	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/>	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> 0 1 2 3 4 5 <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> 6 7 8 9 10
5	----	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/>	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> 0 1 2 3 4 5 <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> 6 7 8 9 10
6	----	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/>	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> 0 1 2 3 4 5 <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> 6 7 8 9 10
7	----	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/>	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> 0 1 2 3 4 5 <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> 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	----	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/>	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> 0 1 2 3 4 5 <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> 6 7 8 9 10
2	----	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/>	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> 0 1 2 3 4 5 <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> 6 7 8 9 10
3	----	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/>	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> 0 1 2 3 4 5 <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> 6 7 8 9 10
4	----	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/>	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> 0 1 2 3 4 5 <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> 6 7 8 9 10
5	----	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/>	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> 0 1 2 3 4 5 <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> 6 7 8 9 10
6	----	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/>	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> 0 1 2 3 4 5 <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> 6 7 8 9 10
7	----	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/>	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> 0 1 2 3 4 5 <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> 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	----	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/>	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> 0 1 2 3 4 5 <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> 6 7 8 9 10
2	----	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/>	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> 0 1 2 3 4 5 <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> 6 7 8 9 10
3	----	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/>	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> 0 1 2 3 4 5 <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> 6 7 8 9 10
4	----	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/>	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> 0 1 2 3 4 5 <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> 6 7 8 9 10
5	----	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/>	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> 0 1 2 3 4 5 <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> 6 7 8 9 10
6	----	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/>	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> 0 1 2 3 4 5 <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> 6 7 8 9 10
7	----	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/>	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> 0 1 2 3 4 5 <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> 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	----	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/>	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> 0 1 2 3 4 5 <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> 6 7 8 9 10
2	----	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/>	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> 0 1 2 3 4 5 <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> 6 7 8 9 10
3	----	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/>	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> 0 1 2 3 4 5 <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> 6 7 8 9 10
4	----	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/>	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> 0 1 2 3 4 5 <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> 6 7 8 9 10
5	----	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/>	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> 0 1 2 3 4 5 <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> 6 7 8 9 10
6	----	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/>	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> 0 1 2 3 4 5 <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> 6 7 8 9 10
7	----	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/>	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> 0 1 2 3 4 5 <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> 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	----	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/>	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> 0 1 2 3 4 5 <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> 6 7 8 9 10
2	----	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/>	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> 0 1 2 3 4 5 <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> 6 7 8 9 10
3	----	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/>	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> 0 1 2 3 4 5 <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> 6 7 8 9 10
4	----	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/>	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> 0 1 2 3 4 5 <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> 6 7 8 9 10
5	----	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/>	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> 0 1 2 3 4 5 <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> 6 7 8 9 10
6	----	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/>	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> 0 1 2 3 4 5 <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> 6 7 8 9 10
7	----	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/>	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> 0 1 2 3 4 5 <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> 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	----	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/>	<input type="checkbox"/> 0 <input type="checkbox"/> 1 <input type="checkbox"/> 2 <input type="checkbox"/> 3 <input type="checkbox"/> 4 <input type="checkbox"/> 5 <input type="checkbox"/> 6 <input type="checkbox"/> 7 <input type="checkbox"/> 8 <input type="checkbox"/> 9 <input type="checkbox"/> 10
2	----	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/>	<input type="checkbox"/> 0 <input type="checkbox"/> 1 <input type="checkbox"/> 2 <input type="checkbox"/> 3 <input type="checkbox"/> 4 <input type="checkbox"/> 5 <input type="checkbox"/> 6 <input type="checkbox"/> 7 <input type="checkbox"/> 8 <input type="checkbox"/> 9 <input type="checkbox"/> 10
3	----	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/>	<input type="checkbox"/> 0 <input type="checkbox"/> 1 <input type="checkbox"/> 2 <input type="checkbox"/> 3 <input type="checkbox"/> 4 <input type="checkbox"/> 5 <input type="checkbox"/> 6 <input type="checkbox"/> 7 <input type="checkbox"/> 8 <input type="checkbox"/> 9 <input type="checkbox"/> 10
4	----	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/>	<input type="checkbox"/> 0 <input type="checkbox"/> 1 <input type="checkbox"/> 2 <input type="checkbox"/> 3 <input type="checkbox"/> 4 <input type="checkbox"/> 5 <input type="checkbox"/> 6 <input type="checkbox"/> 7 <input type="checkbox"/> 8 <input type="checkbox"/> 9 <input type="checkbox"/> 10
5	----	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/>	<input type="checkbox"/> 0 <input type="checkbox"/> 1 <input type="checkbox"/> 2 <input type="checkbox"/> 3 <input type="checkbox"/> 4 <input type="checkbox"/> 5 <input type="checkbox"/> 6 <input type="checkbox"/> 7 <input type="checkbox"/> 8 <input type="checkbox"/> 9 <input type="checkbox"/> 10
6	----	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/>	<input type="checkbox"/> 0 <input type="checkbox"/> 1 <input type="checkbox"/> 2 <input type="checkbox"/> 3 <input type="checkbox"/> 4 <input type="checkbox"/> 5 <input type="checkbox"/> 6 <input type="checkbox"/> 7 <input type="checkbox"/> 8 <input type="checkbox"/> 9 <input type="checkbox"/> 10
7	----	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/>	<input type="checkbox"/> 0 <input type="checkbox"/> 1 <input type="checkbox"/> 2 <input type="checkbox"/> 3 <input type="checkbox"/> 4 <input type="checkbox"/> 5 <input type="checkbox"/> 6 <input type="checkbox"/> 7 <input type="checkbox"/> 8 <input type="checkbox"/> 9 <input type="checkbox"/> 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 treatment	Blood Pressure (mmHg)	Pain (check the number that best represents the maximum pain you experience during the session, if any)
1	----	AM	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/>	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> 0 1 2 3 4 5 <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> 6 7 8 9 10
		PM	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/>	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> 0 1 2 3 4 5 <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> 6 7 8 9 10
2		AM	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/>	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> 0 1 2 3 4 5 <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> 6 7 8 9 10
		PM	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/>	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> 0 1 2 3 4 5 <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> 6 7 8 9 10
3		AM	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/>	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> 0 1 2 3 4 5 <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> 6 7 8 9 10
		PM	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/>	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> 0 1 2 3 4 5 <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> 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 treatment	Blood Pressure (mmHg)	Pain (check the number that best represents the maximum pain you experience during the session, if any)
4	---	AM	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/>	<input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> 0 1 2 3 4 5 <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> 6 7 8 9 10
		PM	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/>	<input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> 0 1 2 3 4 5 <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> 6 7 8 9 10
5	---	AM	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/>	<input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> 0 1 2 3 4 5 <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> 6 7 8 9 10
		PM	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/>	<input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> 0 1 2 3 4 5 <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> 6 7 8 9 10
6	---	AM	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/>	<input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> 0 1 2 3 4 5 <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> 6 7 8 9 10
		PM	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/>	<input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> 0 1 2 3 4 5 <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> 6 7 8 9 10
7	---	AM	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/>	<input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> 0 1 2 3 4 5 <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> 6 7 8 9 10
		PM	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/>	<input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> 0 1 2 3 4 5 <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> 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 treatment	Blood Pressure (mmHg)	Pain (check the number that best represents the maximum pain you experience during the session, if any)
1	----	AM	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/>	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> 0 1 2 3 4 5 <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> 6 7 8 9 10
		PM	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/>	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> 0 1 2 3 4 5 <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> 6 7 8 9 10
2		AM	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/>	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> 0 1 2 3 4 5 <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> 6 7 8 9 10
		PM	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/>	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> 0 1 2 3 4 5 <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> 6 7 8 9 10
3		AM	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/>	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> 0 1 2 3 4 5 <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> 6 7 8 9 10
		PM	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/>	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> 0 1 2 3 4 5 <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> 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 treatment	Blood Pressure (mmHg)	Pain (check the number that best represents the maximum pain you experience during the session, if any)
4	----	AM	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/>	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> 0 1 2 3 4 5 <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> 6 7 8 9 10
		PM	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/>	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> 0 1 2 3 4 5 <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> 6 7 8 9 10
5	----	AM	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/>	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> 0 1 2 3 4 5 <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> 6 7 8 9 10
		PM	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/>	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> 0 1 2 3 4 5 <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> 6 7 8 9 10
6	----	AM	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/>	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> 0 1 2 3 4 5 <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> 6 7 8 9 10
		PM	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/>	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> 0 1 2 3 4 5 <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> 6 7 8 9 10
7	----	AM	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/>	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> 0 1 2 3 4 5 <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> 6 7 8 9 10
		PM	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/>	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> 0 1 2 3 4 5 <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> 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 treatment	Blood Pressure (mmHg)	Pain (check the number that best represents the maximum pain you experience during the session, if any)
1	----	AM	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/>	<input type="checkbox"/> 0 <input type="checkbox"/> 1 <input type="checkbox"/> 2 <input type="checkbox"/> 3 <input type="checkbox"/> 4 <input type="checkbox"/> 5 <input type="checkbox"/> 6 <input type="checkbox"/> 7 <input type="checkbox"/> 8 <input type="checkbox"/> 9 <input type="checkbox"/> 10
		PM	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/>	<input type="checkbox"/> 0 <input type="checkbox"/> 1 <input type="checkbox"/> 2 <input type="checkbox"/> 3 <input type="checkbox"/> 4 <input type="checkbox"/> 5 <input type="checkbox"/> 6 <input type="checkbox"/> 7 <input type="checkbox"/> 8 <input type="checkbox"/> 9 <input type="checkbox"/> 10
2		AM	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/>	<input type="checkbox"/> 0 <input type="checkbox"/> 1 <input type="checkbox"/> 2 <input type="checkbox"/> 3 <input type="checkbox"/> 4 <input type="checkbox"/> 5 <input type="checkbox"/> 6 <input type="checkbox"/> 7 <input type="checkbox"/> 8 <input type="checkbox"/> 9 <input type="checkbox"/> 10
		PM	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/>	<input type="checkbox"/> 0 <input type="checkbox"/> 1 <input type="checkbox"/> 2 <input type="checkbox"/> 3 <input type="checkbox"/> 4 <input type="checkbox"/> 5 <input type="checkbox"/> 6 <input type="checkbox"/> 7 <input type="checkbox"/> 8 <input type="checkbox"/> 9 <input type="checkbox"/> 10
3		AM	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/>	<input type="checkbox"/> 0 <input type="checkbox"/> 1 <input type="checkbox"/> 2 <input type="checkbox"/> 3 <input type="checkbox"/> 4 <input type="checkbox"/> 5 <input type="checkbox"/> 6 <input type="checkbox"/> 7 <input type="checkbox"/> 8 <input type="checkbox"/> 9 <input type="checkbox"/> 10
		PM	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/>	<input type="checkbox"/> 0 <input type="checkbox"/> 1 <input type="checkbox"/> 2 <input type="checkbox"/> 3 <input type="checkbox"/> 4 <input type="checkbox"/> 5 <input type="checkbox"/> 6 <input type="checkbox"/> 7 <input type="checkbox"/> 8 <input type="checkbox"/> 9 <input type="checkbox"/> 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 treatment	Blood Pressure (mmHg)	Pain (check the number that best represents the maximum pain you experience during the session, if any)
4	---	AM	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/>	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> 0 1 2 3 4 5 <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> 6 7 8 9 10
		PM	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/>	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> 0 1 2 3 4 5 <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> 6 7 8 9 10
5	---	AM	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/>	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> 0 1 2 3 4 5 <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> 6 7 8 9 10
		PM	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/>	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> 0 1 2 3 4 5 <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> 6 7 8 9 10
6	---	AM	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/>	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> 0 1 2 3 4 5 <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> 6 7 8 9 10
		PM	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/>	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> 0 1 2 3 4 5 <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> 6 7 8 9 10
7	---	AM	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/>	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> 0 1 2 3 4 5 <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> 6 7 8 9 10
		PM	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/>	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> 0 1 2 3 4 5 <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> 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 treatment	Blood Pressure (mmHg)	Pain (check the number that best represents the maximum pain you experience during the session, if any)
1	----	AM	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/>	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> 0 1 2 3 4 5 <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> 6 7 8 9 10
		PM	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/>	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> 0 1 2 3 4 5 <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> 6 7 8 9 10
2		AM	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/>	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> 0 1 2 3 4 5 <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> 6 7 8 9 10
		PM	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/>	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> 0 1 2 3 4 5 <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> 6 7 8 9 10
3		AM	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/>	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> 0 1 2 3 4 5 <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> 6 7 8 9 10
		PM	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/>	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> 0 1 2 3 4 5 <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> 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 treatment	Blood Pressure (mmHg)	Pain (check the number that best represents the maximum pain you experience during the session, if any)
4	---	AM	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/>	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> 0 1 2 3 4 5 <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> 6 7 8 9 10
		PM	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/>	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> 0 1 2 3 4 5 <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> 6 7 8 9 10
5	---	AM	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/>	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> 0 1 2 3 4 5 <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> 6 7 8 9 10
		PM	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/>	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> 0 1 2 3 4 5 <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> 6 7 8 9 10
6	---	AM	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/>	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> 0 1 2 3 4 5 <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> 6 7 8 9 10
		PM	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/>	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> 0 1 2 3 4 5 <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> 6 7 8 9 10
7	---	AM	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/>	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> 0 1 2 3 4 5 <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> 6 7 8 9 10
		PM	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/>	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> 0 1 2 3 4 5 <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> 6 7 8 9 10



CRU #044 TRIC VCI

Plate #043

Follow Up

Subject ID:

Centre Subject ID

Date:

y y y y m m d d

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

Date that the week started on:

y y y y m m d d

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 treatment	Blood Pressure (mmHg)	Pain (check the number that best represents the maximum pain you experience during the session, if any)
1	----	AM	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/>	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> 0 1 2 3 4 5 <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> 6 7 8 9 10
		PM	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/>	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> 0 1 2 3 4 5 <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> 6 7 8 9 10
2		AM	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/>	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> 0 1 2 3 4 5 <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> 6 7 8 9 10
		PM	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/>	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> 0 1 2 3 4 5 <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> 6 7 8 9 10
3		AM	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/>	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> 0 1 2 3 4 5 <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> 6 7 8 9 10
		PM	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/>	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> 0 1 2 3 4 5 <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> 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 treatment	Blood Pressure (mmHg)	Pain (check the number that best represents the maximum pain you experience during the session, if any)
4	-----	AM	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/>	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> 0 1 2 3 4 5 <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> 6 7 8 9 10
		PM	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/>	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> 0 1 2 3 4 5 <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> 6 7 8 9 10
5	-----	AM	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/>	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> 0 1 2 3 4 5 <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> 6 7 8 9 10
		PM	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/>	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> 0 1 2 3 4 5 <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> 6 7 8 9 10
6	-----	AM	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/>	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> 0 1 2 3 4 5 <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> 6 7 8 9 10
		PM	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/>	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> 0 1 2 3 4 5 <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> 6 7 8 9 10
7	-----	AM	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/>	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> 0 1 2 3 4 5 <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> 6 7 8 9 10
		PM	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/>	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> 0 1 2 3 4 5 <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> 6 7 8 9 10



CRU #044 TRIC VCI

Plate #045

Randomization

Subject ID:

Centre

Subject ID

Date:

y y y y

m m

d d

RANDOMIZATION

Was informed consent obtained?	<input type="checkbox"/> Yes	<input type="checkbox"/> No
Is the participant eligible for randomization?	<input type="checkbox"/> Yes	<input type="checkbox"/> No
Randomization assignment	<input type="checkbox"/> Once Daily Treatment	<input type="checkbox"/> Twice Daily Treatment

Signature: _____

Date:

y y y y

m m

d d



CRU #044 TRIC VCI

Plate #046

Phone Follow Up

Subject ID:

Centre

Subject ID

Date:

y y y y

m m

d d

DAY 2 PHONE VISIT

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

5. Complete the visit checklist:

Review device instructions

Review diary instructions

COMMENTS (optional)

Signature: _____

Date:

y y y y

m m

d d



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):	<input type="checkbox"/> Yes	<input type="checkbox"/> No
2. Has the subject attempted to use the device:	<input type="checkbox"/> Yes	<input type="checkbox"/> No
3. Does the subject report any problems with using the device:	<input type="checkbox"/> Yes	<input type="checkbox"/> No
4. Is the subject willing to continue to participate in the study:	<input type="checkbox"/> Yes	<input type="checkbox"/> No

5. Complete the visit checklist:

Review device instructions	<input type="checkbox"/>
Review diary instructions	<input type="checkbox"/>

COMMENTS (optional)

Signature: _____ Date:
yyyy mm dd



CRU #044 TRIC VCI

Plate #048

Follow Up

Subject ID:

Centre

Subject ID

Date:

yyyy

mm

dd

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:

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 #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	<input type="checkbox"/>
Retrieve patient diary	<input type="checkbox"/>

Signature: _____ Date:

yyyy mm dd

For peer review only



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:	<input type="checkbox"/> Yes	<input type="checkbox"/> No	<input type="checkbox"/> Other: _____
Trail-making part A time to completion (seconds):	<input type="text"/> <input type="text"/> <input type="text"/>		
Trail-making part B completed:	<input type="checkbox"/> Yes	<input type="checkbox"/> No	<input type="checkbox"/> Other: _____
Trail-making part B time to completion (seconds):	<input type="text"/> <input type="text"/> <input type="text"/>		
10-item word list learning completed:	<input type="checkbox"/> Yes	<input type="checkbox"/> No	<input type="checkbox"/> Other: _____
Trial 1 immediate recall:	<input type="text"/> <input type="text"/>		
Trial 1 intrusions:	<input type="text"/> <input type="text"/>		
Trial 2 immediate recall:	<input type="text"/> <input type="text"/>		
Trial 2 intrusions:	<input type="text"/> <input type="text"/>		
Trial 3 immediate recall:	<input type="text"/> <input type="text"/>		
Trial 3 intrusions:	<input type="text"/> <input type="text"/>		
Letter A fluency completed:	<input type="checkbox"/> Yes	<input type="checkbox"/> No	<input type="checkbox"/> Other: _____
Letter A fluency number of words:	<input type="text"/> <input type="text"/>		
Letter S fluency completed:	<input type="checkbox"/> Yes	<input type="checkbox"/> No	<input type="checkbox"/> Other: _____
Letter S fluency number of words:	<input type="text"/> <input type="text"/>		
Animal fluency completed:	<input type="checkbox"/> Yes	<input type="checkbox"/> No	<input type="checkbox"/> Other: _____
Animal fluency number of words:	<input type="text"/> <input type="text"/>		



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:

<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>
<i>Centre</i>		<i>Subject ID</i>			

Date:

<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>
<i>y y y y</i>				<i>m m</i>		<i>d d</i>	

MRI TRANSMITTAL

Date of MRI:	<table border="1"> <tr> <td><input type="text"/></td> <td><input type="text"/></td> <td><input type="text"/></td> <td><input type="text"/></td> <td><input type="text"/></td> <td><input type="text"/></td> <td><input type="text"/></td> <td><input type="text"/></td> </tr> <tr> <td colspan="4" style="text-align: center;"><i>y y y y</i></td> <td colspan="2" style="text-align: center;"><i>m m</i></td> <td colspan="2" style="text-align: center;"><i>d d</i></td> </tr> </table>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<i>y y y y</i>				<i>m m</i>		<i>d d</i>	
<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>										
<i>y y y y</i>				<i>m m</i>		<i>d d</i>											
MRI transmitted:	<input type="checkbox"/> Yes <input type="checkbox"/> No																
If no, give reason:																	
<input type="checkbox"/> No longer participating in the study (study termination CRF should also have been completed) <input type="checkbox"/> Participant declined <input type="checkbox"/> Not completed due to claustrophobia <input type="checkbox"/> MRI contraindication <input type="checkbox"/> MRI technical problem <input type="checkbox"/> Other reason: _____																	

Signature: _____	Date:	<table border="1"> <tr> <td><input type="text"/></td> <td><input type="text"/></td> <td><input type="text"/></td> <td><input type="text"/></td> <td><input type="text"/></td> <td><input type="text"/></td> <td><input type="text"/></td> <td><input type="text"/></td> </tr> <tr> <td colspan="4" style="text-align: center;"><i>y y y y</i></td> <td colspan="2" style="text-align: center;"><i>m m</i></td> <td colspan="2" style="text-align: center;"><i>d d</i></td> </tr> </table>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<i>y y y y</i>				<i>m m</i>		<i>d d</i>	
<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>											
<i>y y y y</i>				<i>m m</i>		<i>d d</i>												



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 # <input type="text"/>	Adverse Event term _____		
AE Start Date:	<input type="text"/>	<input type="text"/>	<input type="text"/>
	yyyy	mm	dd
AE End Date (or Continuing):	<input type="text"/>	<input type="text"/>	<input type="text"/>
	yyyy	mm	dd
	<input type="checkbox"/> Continuing		
Outcome:	<input type="checkbox"/> Fatal	<input type="checkbox"/> Not recovered/ not resolved	<input type="checkbox"/> Recovered w/sequelae
	<input type="checkbox"/> Recovered w/o sequelae	<input type="checkbox"/> Recovering/ resolving	
Severity/Grade:	<input type="checkbox"/> Mild	<input type="checkbox"/> Moderate	<input type="checkbox"/> Severe
Is the Event Serious?	<input type="checkbox"/> Yes (Complete SAE)		<input type="checkbox"/> No
Is the Event Expected?	<input type="checkbox"/> Yes		<input type="checkbox"/> No
AE Treatment:	<input type="checkbox"/> None	<input type="checkbox"/> Medication(s)	<input type="checkbox"/> Non-medication TX
Action Taken with Study Intervention:	<input type="checkbox"/> None	<input type="checkbox"/> Interrupted	<input type="checkbox"/> Discontinued
	<input type="checkbox"/> Device sessions reduced	<input type="checkbox"/> Device sessions increased	<input type="checkbox"/> Not Applicable
Attribution/Relatedness:	<input type="checkbox"/> Definite	<input type="checkbox"/> Probable	<input type="checkbox"/> Possible
	<input type="checkbox"/> Unlikely	<input type="checkbox"/> 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 # <input type="text"/>	Site Adverse Event term
	Common sense Adverse Event term
AE Category: <small>(Please look up corresponding AE Category at :https://safetyprofiler-ctep.nci.nih.gov/)</small>	

	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 # <input type="text"/>	Serious Adverse Event term <hr/>
Report Type	<input type="checkbox"/> Initial Report <input type="checkbox"/> Follow-up Report F/U Report # <input type="text"/> <input type="checkbox"/> Final Report
SAE Classification:	<input type="checkbox"/> Fatal (resulted in death)
	<input type="checkbox"/> A life-threatening occurrence
	<input type="checkbox"/> Requires inpatient hospitalization or prolongation of existing hospitalization
	<input type="checkbox"/> Results in persistent or significant disability/incapacity
	<input type="checkbox"/> Results in congenital anomaly/birth defect
	<input type="checkbox"/> 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.
	<input type="checkbox"/> 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:	<input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> yyyy mm dd
SAE End Date (or Continuing):	<input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> yyyy mm dd <input type="checkbox"/> Continuing
Grade:	<input type="checkbox"/> Mild <input type="checkbox"/> Moderate <input type="checkbox"/> Severe <input type="checkbox"/> Life Threatening <input type="checkbox"/> Death (Fatal)
Is the Event Expected?	<input type="checkbox"/> Yes <input type="checkbox"/> 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:	<input type="checkbox"/> Definite	<input type="checkbox"/> Probable	<input type="checkbox"/> Possible
	<input type="checkbox"/> Unlikely	<input type="checkbox"/> Unrelated	
Outcome:	<input type="checkbox"/> Fatal	<input type="checkbox"/> Not recovered/ not resolved	<input type="checkbox"/> Recovered w/sequelae
	<input type="checkbox"/> Recovered w/o sequelae	<input type="checkbox"/> Recovering/ resolving	
Lead Site Notified Date:	<input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/>	<input type="text"/> <input type="text"/>	<input type="text"/> <input type="text"/>
	y y y y	m m	d d
Local IRB/REB Notified Date:	<input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/>	<input type="text"/> <input type="text"/>	<input type="text"/> <input type="text"/>
	y y y y	m m	d d
Narrative/Details:	<hr/>		

Signature of investigator confirms 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:

y y y y

m m

d d

SAFETY ADJUDICATION (SAE)

REPORT INFORMATION

Serious Adverse Event Name _____

SAE Start Date

y y y y m m d d

SAE End Date (or Continuing):

y y y y m m d d

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:

Review only



CRU #044 TRIC VCI

Plate #061

Pg#:

Subject ID:

Centre

Subject ID

Date:

y y y y

m m

d d

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: _____

Review only



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: <input type="text"/> <input type="text"/> <input type="text"/> . <input type="text"/> <input type="text"/>	
Indication: _____		Units: <input type="checkbox"/> mg <input type="checkbox"/> mcg <input type="checkbox"/> mL <input type="checkbox"/> cc <input type="checkbox"/> IU <input type="checkbox"/> mEq <input type="checkbox"/> oz <input type="checkbox"/> tsp <input type="checkbox"/> tbl <input type="checkbox"/> gtt	
Route:	<input type="checkbox"/> po <input type="checkbox"/> pr <input type="checkbox"/> sub-q <input type="checkbox"/> sub-lingual <input type="checkbox"/> IM <input type="checkbox"/> IV <input type="checkbox"/> Patch <input type="checkbox"/> Topical <input type="checkbox"/> Nasal <input type="checkbox"/> Other: _____		
Frequency:	<input type="checkbox"/> OD <input type="checkbox"/> BID <input type="checkbox"/> TID <input type="checkbox"/> QID <input type="checkbox"/> PRN <input type="checkbox"/> Other: _____		
Start Date:	<input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <p style="text-align: center;">yyyy mm dd</p>		
End Date:	<input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <p style="text-align: center;">yyyy mm dd</p> OR <input type="checkbox"/> Unable to determine		

Medication Name: _____		Dose: <input type="text"/> <input type="text"/> <input type="text"/> . <input type="text"/> <input type="text"/>	
Indication: _____		Units: <input type="checkbox"/> mg <input type="checkbox"/> mcg <input type="checkbox"/> mL <input type="checkbox"/> cc <input type="checkbox"/> IU <input type="checkbox"/> mEq <input type="checkbox"/> oz <input type="checkbox"/> tsp <input type="checkbox"/> tbl <input type="checkbox"/> gtt	
Route:	<input type="checkbox"/> po <input type="checkbox"/> pr <input type="checkbox"/> sub-q <input type="checkbox"/> sub-lingual <input type="checkbox"/> IM <input type="checkbox"/> IV <input type="checkbox"/> Patch <input type="checkbox"/> Topical <input type="checkbox"/> Nasal <input type="checkbox"/> Other: _____		
Frequency:	<input type="checkbox"/> OD <input type="checkbox"/> BID <input type="checkbox"/> TID <input type="checkbox"/> QID <input type="checkbox"/> PRN <input type="checkbox"/> Other: _____		
Start Date:	<input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <p style="text-align: center;">yyyy mm dd</p>		
End Date:	<input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <p style="text-align: center;">yyyy mm dd</p> OR <input type="checkbox"/> Unable to determine		

Signature: _____ Date:

yyyy mm dd



CRU #044 TRIC VCI

Plate #063

Randomization

Subject ID:

Centre Subject ID

Date:

y y y y m m d d

DEVICE PROVISION

1. Randomization and device provision checklist:	<input type="checkbox"/> Subject randomized		
	<input type="checkbox"/> Device provided		
	<input type="checkbox"/> Device instructions provided		
	<input type="checkbox"/> Subject diary provided		
	<input type="checkbox"/> Device training provided		
2. First treatment cycle:	<input type="checkbox"/> Completed	<input type="checkbox"/> 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:	<input type="text"/> <input type="text"/>	[range 0-10]
	3.b. Pain level during the last cuff inflation of the cycle:	<input type="text"/> <input type="text"/>	[range 0-10]
4. Symptoms reported during treatment (check all that apply):			
Was the treatment painful?	<input type="checkbox"/> Yes	<input type="checkbox"/> No	<input type="checkbox"/> Not sure
Was there tingling (paresthesia)?	<input type="checkbox"/> Yes	<input type="checkbox"/> No	<input type="checkbox"/> Not sure
5. Other symptoms during treatment:			
<input type="text"/> <input type="text"/> <input type="text"/>			
6. Is subject willing to continue in the study:	<input type="checkbox"/> Yes	<input type="checkbox"/> No	
If "No", then subject will not continue in the study. Complete CRF Study Drop Out.			
Signature: _____	Date:	<input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/>	<input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/>
		y y y y	m m d d

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.

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2
3 All study investigators at the clinical sites must ensure that the confidentiality of personal
4 identity and all personal medical information of study participants are maintained at all
5 times. Federal legislation in Canada (Personal Information Protection and Electronic
6 Documents Act – PIPEDA), and provincial legislation (eg. Health Information Act – HIA in
7 Alberta) where applicable, must be followed. Additionally, any U.S. clinical sites must follow
8 privacy obligations to study participants under the Health Insurance Portability and
9 Accountability Act (HIPAA). European or Asian/Australasian sites must conform to local
10 privacy and confidentiality law and custom. On the CRFs and other study documents or
11 image materials submitted to the CRU, the subjects are identified only by study
12 identification code.
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19 Personal medical information may be reviewed for the purpose of verifying data recorded
20 in the CRF by the site monitors. Other properly authorized persons, such as the regulatory
21 authorities, may also have access to these records. Personal medical information is
22 always treated as confidential.
23
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27

28 **Audit and inspection**

29 The Sponsor-Investigator and any Participating Site Investigators should understand that
30 source documents for this trial should be made available to appropriately qualified
31 personnel from the Sponsor-Investigator or designee after appropriate notification. The
32 verification of the CRF data must be by direct inspection of source documents.
33
34
35
36

37 Any Participating Site Investigators shall supply the Sponsor-Investigator on request with
38 any required background data from the study documentation or clinic records. This is
39 particularly important when CRFs are illegible or when errors in data transcription are
40 suspected. In case of special problems and/or governmental queries or requests for audit
41 inspections, it is also necessary to have access to the complete study records, provided
42 that subject confidentiality is protected.
43
44
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48 **Archiving**

49 The Sponsor-Investigator (and any Participating Site Investigators) must keep both (1)
50 Investigator's Study Files and (2) subject clinical source documents on file according to local
51 clinical trial regulation. For example, at the University of Calgary, for non-Health Canada
52 regulated studies, that period is 5 years from the time of official closure of the study. After that
53 period of time the documents may be destroyed, subject to local regulations.
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5 Data sharing policies will follow the spirit of the National Institute of Health (NIH) policy
6 [\[http://grants2.nih.gov/grants/policy/data_sharing/data_sharing_guidance.htm\]](http://grants2.nih.gov/grants/policy/data_sharing/data_sharing_guidance.htm). A similar
7 policy is in place at the Canadian Institutes of Health Research (CIHR). In addition, the
8 Executive Committee will follow the CIHR guidelines on public access to trial results and
9 make the results available as free-access using PubMed. Upon completion of the trial, a
10 public use database will be prepared by stripping any and all personal identifiers. The
11 public use database, consisting of several data files, should contain: (1) baseline and
12 demographic characteristics; (2) outcomes assessments; (3) MRI data; (4) cognitive data;
13 (5) concomitant medications; and (6) adverse events. Each data file is made available as a
14 formatted text file or other electronic format. The data files are distributed along with the
15 data dictionary and a brief instruction (“Readme”) file. These data files will be made
16 available to the public one year after completion of follow-up for the last subject.
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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

1	Introduction			
2				
3	Background and	6a	Description of research question and justification for undertaking the trial, including summary of relevant	___5-7___
4	rationale		studies (published and unpublished) examining benefits and harms for each intervention	
5				
6		6b	Explanation for choice of comparators	___7___
7				
8	Objectives	7	Specific objectives or hypotheses	___7___
9				
10	Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group),	
11			allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	___8___
12				
13				
14	Methods: Participants, interventions, and outcomes			
15				
16	Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will	___13___
17			be collected. Reference to where list of study sites can be obtained	
18				
19	Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and	___10___
20			individuals who will perform the interventions (eg, surgeons, psychotherapists)	
21				
22	Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be	___8-9___
23			administered	
24				
25		11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose	___9___
26			change in response to harms, participant request, or improving/worsening disease)	
27				
28		11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence	___11___
29			(eg, drug tablet return, laboratory tests)	
30				
31		11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	___10___
32				
33	Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood	___12___
34			pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg,	
35			median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen	
36			efficacy and harm outcomes is strongly recommended	
37				
38	Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for	___12___
39			participants. A schematic diagram is highly recommended (see Figure)	
40				
41				
42				
43				
44				
45				
46				

1 Sample size 14 Estimated number of participants needed to achieve study objectives and how it was determined, including _____12_____
 2 clinical and statistical assumptions supporting any sample size calculations

3
 4 Recruitment 15 Strategies for achieving adequate participant enrolment to reach target sample size _____12_____
 5

6 **Methods: Assignment of interventions (for controlled trials)**

7
 8 Allocation:

9
 10 Sequence 16a Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any _____9_____
 11 generation factors for stratification. To reduce predictability of a random sequence, details of any planned restriction
 12 (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants
 13 or assign interventions
 14

15
 16 Allocation 16b Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, _____9_____
 17 concealment opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned
 18 mechanism
 19

20
 21 Implementation 16c Who will generate the allocation sequence, who will enrol participants, and who will assign participants to _____16_____
 22 interventions
 23

24 Blinding (masking) 17a Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome _____9_____
 25 assessors, data analysts), and how
 26

27 17b If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's _____9_____
 28 allocated intervention during the trial
 29
 30

31 **Methods: Data collection, management, and analysis**

32
 33 Data collection 18a Plans for assessment and collection of outcome, baseline, and other trial data, including any related _____10-11,
 34 methods processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of Supplement 2
 35 study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known.
 36 Reference to where data collection forms can be found, if not in the protocol
 37

38
 39 18b Plans to promote participant retention and complete follow-up, including list of any outcome data to be _____12_____
 40 collected for participants who discontinue or deviate from intervention protocols
 41
 42

1	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
2				
3				
4				
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 ___
6				
7				
8		20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	___ 14 ___
9				
10		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 ___
11				
12				
13				
14	Methods: Monitoring			
15				
16	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
17				
18				
19				
20				
21				
22		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__
23				
24				
25	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 ___
26				
27				
28	Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	___ 17 ___
29				
30				
31				
32	Ethics and dissemination			
33				
34	Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	___ 16 ___
35				
36				
37	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 ___
38				
39				
40				
41				
42				

1	Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	_____16_____
2				
3				
4		26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	_____16_____
5				
6				
7	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_____
8				
9				
10	Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	_____16_____
11				
12				
13	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_____
14				
15				
16				
17	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_
18				
19				
20	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_____
21				
22				
23				
24		31b	Authorship eligibility guidelines and any intended use of professional writers	_supplement 5
25				
26		31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	_____18_____
27				
28				
29	Appendices			
30				
31	Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	_supplement 4
32				
33				
34	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
35				
36				

*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](https://creativecommons.org/licenses/by-nc-nd/3.0/)" license.