SUPPLEMENTARY FILE 2: DETAILS OF STUDY ASSESSMENTS AT EACH VISIT

Screening visit

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

The screening visit assessment are:

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

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

Randomization visit

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

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

Physical examination: NIH Stroke Scale score, arm examination.

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

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

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

		Total 18-20 minutes

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

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

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

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

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

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

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

MRI Sequence Parameters

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

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

Day 1-3 telephone follow-up visit

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

Day 15 telephone follow-up visit

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

Day 30 in-person follow-up visit

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

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

90-day in-person follow-up visit

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

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

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

Exit Interview

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