

Supplementary material 1. Ongoing Studies of Remote Ischaemic Conditioning (RIC) in Stroke

Study	Status	Population	N	RIC Protocol	Control Group(s)	Primary Outcome	Selected Secondary Outcome Measures
REMOTE ISCHAEMIC PRE-CONDITIONING							
NEAT (NCT03496415) China 2018-19	Recruiting	Unruptured CA pre-ET	210	Unspecified cycle length (200mmHg)	Sham RIC (60mmHg)	New DWI lesions day 3	Ischaemic lesion burden NIHSS day 7 mRS day 30
NCT03814850 USA 2019-22	Not yet recruiting	Unruptured CA pre-ET	50	4 x 5 mins (30mmHg > SBP) Unilateral UL	Sham RIC (30mmHg)	Adverse events	Cognitive impairment day 2-4 and 9 months Ischaemic lesion volume day 2-4
RIPAT (NCT02162654) ²⁶ Austria 2013-16	Unknown	Unruptured CA pre- ET/surgery	48	3 x 5 mins (200mmHg) Unilateral UL	Sham RIC (10mmHg)	Biomarkers (S100B, NSE, GFAP, MMP9, Microparticles)	New ischaemic lesions day 1- 2 NIHSS and mRS at 12 months
REMOTE ISCHAEMIC PER-CONDITIONING AND/OR EARLY REMOTE ISCHAEMIC POST-CONDITIONING							
RESCUE- BRAIN (NCT02189928) ²⁸ France 2015-19	Completed	AIS	200	4 x 5 mins (110mmHg > SBP) Unilateral LL	Usual medical therapy	DWI MRI infarct volume at 24 hrs	mRS day 90

RICAMIS (NCT03740971) ⁶² China 2018-20	Recruiting	AIS (NIHSS 6-16)	180 0	5 x 5 mins (200mmHg) Bilateral UL Twice daily 10-14 days	Usual care	mRS day 90	NIHSS day 12 Stroke associated pneumonia All cause mortality day 90 Biomarkers (BDNF, VEGF, HIF-1 α , TNF- α , IL-1 β , IL-6)
RESIST (NCT03481777) Denmark 2018-24	Recruiting	AIS and ICH	150 0	5 x 5 mins (200mmHg) Unilateral UL Twice daily up to 7 days	Sham RIC (20mmHg)	mRS day 90	Recurrent ischaemic stroke at 12 months Flow cytometry MicroRNA
PROTECT-I (NCT03915782) France 2019-21	Not yet recruiting	AIS + MT	126	4 x 5 mins (200mmHg) UL	Sham RIC (30mmHg)	Infarct volume day 1 (FLAIR)	NIHSS day 7 mRS day 90
SERIC-sICH (NCT03484936) China 2018-21	Not yet recruiting	Acute sICH	530	4 x 5 mins (200mmHg) UL Twice daily 7 days	Sham RIC	mRS day 90	Adverse events CT haematoma expansion 24 hrs
REVISE-2 (NCT03045055) China 2018-19	Not yet recruiting	AIS + MT	180	4 x 5 mins (200mmHg) Unilateral UL	Sham RIC (60mmHg)	Final CT infarct volume	Trial feasibility mRS day 9 Change in NIHSS
REPOST (NTR6880) ⁶³ Netherlands 2018-21	Recruiting	AIS	200	4 x 5 mins (20mmHg > SBP) Unilateral UL Twice daily up to 4 days	Sham RIC (50mmHg)	MRI DWI infarct volume day 4 (or day of discharge)	NIHSS at discharge mRS day 90 Recurrent vascular events at 12 months
RICH	Recruiting	Acute sICH	40	4 x 5 mins	Usual Care	Adverse events	

(NCT03930940) China 2019-22				(200mmHg) UL			
REMOTE-CAT (NCT03375762) Spain 2019-22	Recruiting	Suspected AIS	572	5 x 5 mins Unspecified cuff pressure Non-paretic UL	Sham RIC (unspecified pressure)	mRS day 90	Early NIHSS change Infarct volume (DWI MRI) Metabolomic and lipidomic biomarkers
SERIC-AIS (NCT03669653) China 2018-22	Recruiting	AIS	912	4 x 5 mins (200mmHg) UL Twice daily Up to 7 days	Sham RIC (60mmHg)	mRS day 90	NIHSS day 7 Inflammatory cytokines
SERICT-AIS (NCT04027621) China 2019-20	Completed	AIS + tPA	50	4 x 5 mins (200mmHg) UL Twice between 6- 24hrs post tPA	Sham RIC (60mmHg)	Adverse events	NIHSS day 7 or discharge mRS day 90
rTPA-RIC (NCT02886390) China 2018-19	Recruiting	AIS + tPA	60	5 x 5 mins (200mmHg) Bilateral UL	tPA alone	MRI DWI infarct volume at 72 hours	NIHSS day 5-7 mRS day 90 Recurrent events day 90 MMP-9, IL-6, HS-CRP at baseline and Day 7
rTPA-RIC1 (NCT03231384) China 2017-18	Completed	AIS + tPA	31	5 x 5 mins (200mmHg) Bilateral UL	tPA alone	Feasibility	Signs of tissue or neurovascular injury Infarct volume (MRI) day 7 NIHSS day 7 mRS day 90
RIC-ACS (NCT03868007)	Not yet recruiting	Age \geq 60 AIS + ACS	80	5 x 5 mins (200mmHg)	Sham RIC (60mmHg)	All cause mortality at 3 months	NIHSS day 90 GRACE score day 90

China 2019				Bilateral UL 14 days			
RIC-SIID (NCT04069546) China 2019-20	Recruiting	AIS	30	5 x 5 mins (180mmHg) Unilateral UL	Usual care	Flow cytometry (immune profile)	Serum cytokines at baseline, day 2 and day 7 (TLR-2, IL- 6) Stroke associated pneumonia
TRIPCAIS (NCT03218293) China 2017-20	Recruiting	AIS + tPA	120	5 x 5 mins (3 min deflations) (Unspecified cuff pressure) Bilateral UL	Usual care	VEGF, bFGF up to 12 months	NIHSS day 14 ADLs day 90
ICARUS (NCT03481205) USA 2018-21	Not yet recruiting	AIS & LVO (helicopter transit)	10	3-5 x 5 mins (200mmHg) Bilateral UL	Usual care	Feasibility	Adverse events
NCT03335111 China 2016-19	Recruiting	AIS	100	5 x 5 mins (50mmHg > SBP) Bilateral UL for 7 days	Sham RIC (60mmHg)	Serum cytokines and peripheral immune cells at baseline, day 1 & day 7.	NIHSS day 7 Recurrent stroke at 12 months
ChiCTR- 1800018290 China 2019-20	Recruiting	AIS & SAH & 'Brain- Heart Syndrome'	60	Not specified	Usual care	Cardiac function (ECG, Echo, serum markers)	mRS at discharge, 30 days and 6 months
DIPIS (ChiCTR- IOR-17012011) China 2017-18	Completed	AIS	44	Not specified	Sham RIC (unspecified pressure)	Stroke progression day 90	mRS, NIHSS, vascular events and mortality day 90
ChiCTR-IOR- 15006549 ⁶⁴	Recruiting	AIS	400	4 x 5 mins (200mmHg)	Sham RIC (30mmHg)	Feasibility	Infarct volume mRS

China 2015-18				Non-paretic UL for 14 days			NIHSS Mortality
NCT03968068 UK 2019-20	Recruiting	AIS	48	4 x 5 mins (200mmHg) Unilateral UL	30 mins AE 30 mins AE in healthy controls RIC 4 x 5 mins in healthy controls	Adverse events Discomfort (Likert Scale) % interventions completed	CBFv (TCD)
ERVAS ⁶⁵ India 2018-present	Recruiting	Aneurysma 1 SAH	24	3 x 5 mins (30mmHg > SBP) UL Every 48 hours up to day 7-10	Sham RIC (30mmHg)	Vasospasm (TCD, angiography) Serum Biomarkers (S100B, NSE)	GOSE at 1, 3 and 6 months
PreLIMBS (NCT02411266) USA 2018-22	Recruiting	Aneurysma 1 SAH	60	3 x 10 mins (5 min deflation) (200mmHg) Unilateral LL every 1-2 days for 14 days	Sham RIC (30mmHg)	Adverse events	mRS day 90
NEAT2 (NCT03561311) China 2018-19	Recruiting	Ruptured CA + ET	210	Unspecified cycles (200mmHg) Bilateral UL	Sham RIC (60mmHg)	Ischaemic lesions (MRI DWI) at 72 hours	NIHSS day 7 Cerebrovascular events day 30

RIPC-SAH (NCT02381522) USA 2015-19	Active, not recruiting	Aneurysma 1 SAH	26	4 cycles (unspecified length) (20mmHg > SBP) Unilateral LL	Sham RIC (20mmHg < SBP)	Vasospasm (TCD)	mRS Mortality Additional neurological events
RICE-PAC (NCT03152799) UK 2017-19	Unknown	AIS (anterior circulation) + MT	60	Unspecified protocol Non-paretic UL	Sham RIC	Penumbral salvage (MRI) at 3 months	Cerebral oedema and infarct size day 7 mRS, NIHSS and QoL at 3 months
ChiCTR-INR- 17012308 China 2017-20	Not yet recruiting	AIS	200	3 x 5 mins (20mmHg > SBP) Unilateral UL	Sham RIC (0mmHg)	Coagulant Function (TEG-MA)	mRS at 12 months Recurrent ischaemic stroke
CHRONIC REMOTE ISCHAEMIC POST-CONDITIONING							
PICNIC-One (NCT03004820) ⁶⁶ China 2016-17	Completed	NDS or high-risk TIA	167	5 x 5 min (200mmHg) Bilateral UL Twice daily 90 days	No comparator	Recurrent stroke/TIA day 90	Compliance Adverse events Handgrip strength in affected arm at day 90 NIHSS, mRS and BI day 90
NCT03635177 Denmark 2019-21	Recruiting	Lacunar stroke	20	Crossover: 4 x 5 mins (200mmHg) Unilateral UL Once daily 4 weeks	Crossover: Sham RIC	FMD (brachial artery)	Femoral artery blood flow before and after exercise CBFv during visual task Platelet reactivity
EPIC-sICAS (NCT02323425) China 2015-18	Unknown	sIntraCAS	100	5 x 3 mins (5 mins deflation) (180mmHg) Bilateral UL	Usual care	Collateral circulation at 6 months (MRA, DCE- MRI, TCD, SPECT)	NIHSS at 1 year VEGF and bFGF day 10

				Twice daily 180 days			
NCT04039399 USA 2019-20	Recruiting	Chronic unilateral stroke with residual lower limb paresis	15	Crossover: 5 x 5 mins (225mmHg) Unilateral LL (Paretic Leg)	Crossover: Sham RIC (10mmHg)	Cold Pressor Test and plasma epinephrine & norepinephrine	SBP after RIC and cold pressor test
NCT04038697 USA 2018-24	Recruiting	Chronic unilateral cortical stroke with residual lower limb paresis	120	5 x 5 mins (225mmHg) Unilateral LL (Paretic Leg) 12 sessions over 4 weeks + Treadmill Training	Sham RIC (10mmHg) + Treadmill Training RIC alone RIC + Treadmill Training (healthy controls)	Self-selected walking speed at 4 weeks (10MWT)	Knee extensor strength FMD of non-paretic brachial artery Heart rate variability
NCT02534545 ²⁹ China 2015-19	Recruiting	Ischaemic stroke or high-risk TIA	300 0	5 x 5 mins (200mmHg) Bilateral UL Once daily 12 months	Sham RIC (60mmHg)	Time to recurrent stroke	All cause mortality NIHSS, mRS and BI at 12 months
RICFAST (NCT03794947) UK 2019-21	Recruiting	Stroke at least 6 weeks prior with disabling fatigue	34	4 x 5 mins (200mmHg) Unilateral UL 18 sessions over 6 weeks	Sham RIC (20 mmHg)	Feasibility Adverse events	FSS 6 weeks Cerebral Perfusion (MRI Perfusion)
ChiCTR-	Recruiting	sIntraCAS	273	5 x 5 min	3 x 3 min	Recurrent stroke/TIA at	NIHSS, mRS and BI at 12

1800014403 China 2018-20				(200mmHg) Bilateral UL Twice daily 12 months	(200mmHg) Bilateral UL Twice daily 12 months Usual Treatment	12 months	months
NCT035890 China 2018-19	Recruiting	sIntraCAS	30	5 x 5 mins (200mmHg) Bilateral UL Twice daily 90 days	Sham RIC	CBF and brain metabolism under stress	Stroke recurrence
PICASSO (NCT03208166) USA 2017-19	Completed	sIntraCAS	2	4 x 5 mins (200mmHg) Bilateral UL Daily 30 days	Usual care	CBF (MRI ASL) day 30 Feasibility	Biomarkers at day 30 (including Nitrite, IL-10, hs- CRP and MMP-9)
REM- PROTECT (NCT02169739) USA 2015-19	Recruiting	≥40 yrs Lacunar stroke	60	4 x 5 mins (Unspecified cuff pressure) Once or twice daily One year	Usual care	Adherence Patient-reported discomfort	
NCT03105141 China 2017-20	Recruiting	sIntraCAS	600	Bilateral UL. 10 treatment groups with varied number of cycles, cycle lengths, frequency and cuff pressure	Several active comparators	Recurrent stroke at 12 months	Adverse events Cerebral perfusion (multi-modal) Cognition (MMSE, MOCA, TICS-M)
ChiCTR190002	Not yet	sIntraCAS	140	Not specified	Sham RIC	NIHSS, mRS & BI day	Vascular events day 180

1006 China 2019	recruiting				(unspecified pressure)	180	CBF at day 180
RIC-CCCA (NCT03721692) China 2018-24	Enrolling by Invitation	sIntraCAS & sCAS	392	5 x 5 mins (Unspecified cuff pressure) UL Once daily 3 months	Usual care	Combined vascular events at 1 year	Time to vascular event All cause mortality at 1 year mRS day 90
NCT02971462 China 2016-17	Unknown	sIntraCAS	80	5 x 5 mins (200mmHg) Bilateral UL Twice daily Unspecified duration	Usual care	Posterior circulation stroke at 6 months	Combined cerebrovascular events at 6 months mRS at 6 months CBF (TCD) at 6 months
ChiCTR-OPC- 17012871 China 2016-18	Unknown	Ischaemic stroke	50	Daily RIC (not further specified)	None	Depression incidence	HDS
UNDETERMINED							
ChiCTR- 1900026034 China 2018-21	Recruiting	AIS	104	Not specified	Usual care	Neuropsychological evaluation P300 event-related potential	ICAM-1 Endothelin-1

Key:

10MWT – 10 meter walk test
 ACS – Acute Coronary Syndrome
 ADL – Activities of daily living
 AE – Aerobic exercise
 AIS – Acute Ischaemic Stroke

AIS + MT – Acute Ischaemic Stroke plus Mechanical Thrombectomy
ASL – Arterial spin-labeled
BDNF – Brain-derived neurotrophic factor
BI – Barthel index
bFGF – Basic Fibroblast Growth Factor
CA – Cerebral aneurysm
CBF(v) – Cerebral blood flow (velocity)
DCE-MRI – Dynamic Contrast-Enhanced Magnetic Resonance Imaging
DWI – Diffusion Weighted Imaging
ET – Endovascular Therapy
FMD – Flow Mediated Dilatation
FSS – Fatigue Severity Score
GOSE – Extended Glasgow Outcome Scale
GFAP – Glial Fibrillary Acidic Protein
HDS – Hamilton Depression Scale
HIF-1 α – Hypoxia-inducible Factor 1-Alpha
HSP – Heat shock proteins
HS-CRP – High Sensitivity C Reactive Protein
ICAM-1 – Intracellular Adhesion Molecule 1
ICH – Intracerebral Haemorrhage
IL-1 β – Interleukin 1 Beta
IL-4 – Interleukin 4
IL-6 – Interleukin 6
IL-10 – Interleukin 10
LL – Lower Limb
LVO – Large Vessel Occlusion
MMP-9 – Matrix metalloproteinase-9
MFI – Multidimensional Fatigue Inventory
MMSE – Mini-Mental State Examination
MOCA – Montreal Cognitive Assessment

mRS – Modified Rankin Scale
NDS – Non-disabling Stroke
NIHSS – National Institutes of Health Stroke Scale
NSE – Neuron-Specific Enolase
QoL – Quality of Life Assessment
S100B – S100 calcium-binding protein B
SAH – Subarachnoid Haemorrhage
SBP – Systolic Blood Pressure
sIntraCAS – Symptomatic Intracranial Atherosclerosis
sCAS – Symptomatic Coronary Artery Stenosis
SPECT – Single Photon Emission Computed Tomography
TCD – Transcranial Doppler
TEG-MA – Thromboelastography
TIA – Transient Ischaemic Attack
TICS-M – Modified Telephone Interview for Cognitive Status

TLR-2 – Toll-like Receptor 2
TNF α – Tumour Necrosis Factor Alpha
tPA – Tissue Plasminogen Activator (Intravenous Thrombolysis)
UL – Upper Limb
VEGF – Vascular Endothelial Growth Factor

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