

Remote Ischaemic Conditioning After Stroke 3

Statistical Analysis Plan

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1. Introduction

This Statistical Analysis Plan (SAP) pre-specifies all analyses to be performed for the RECAST-3 trial. It has been finalised and made publicly available prior to database lock and unblinding. This document should be read alongside the protocol. Any deviation from this SAP at the time of analysis will be documented and transparently reported in the results paper.

RECAST-3 is a multicentre, prospective, 1:1 randomised, sham-controlled, blinded-endpoint, parallel-group, phase III trial of remote ischaemic conditioning (RIC) in adults with acute ischaemic stroke (AIS). The trial was halted early at 272 participants due to sustained recruitment difficulties, which are described in detail in the protocol paper. All pre-specified analyses will be conducted on the available dataset.

Approach to secondary outcomes: Given the reduced sample size (272 vs 1300 planned), hypothesis testing of secondary outcomes carries unacceptably high risks of both false-negative results (low power) and, where multiple outcomes are examined, false-positive results. To avoid misleading conclusions, secondary outcomes will be presented as covariate-adjusted effect estimates with 95% confidence intervals only. No p-values will be calculated or reported for secondary outcomes. This approach follows recommendations for reporting underpowered trials²² and focuses interpretation on the direction and precision of treatment effects rather than dichotomous significance. The primary outcome will be reported with a full hypothesis test (p-value), as pre-specified. Subgroup analyses of the primary outcome will be presented as interaction effects with 95% CIs; given the reduced sample size, interaction p-values are retained for completeness but should be interpreted with caution.

2. Trial Overview

Intervention

Active (RIC): 4 cycles of bilateral upper-arm cuff inflation to +20 mmHg above systolic blood pressure (5 minutes inflation / 5 minutes deflation), twice daily for up to 14 days (maximum 28 doses), commenced within 48 hours of stroke onset. Device: AT4 Electronic Tourniquet System (AneticAid Ltd; CE-marked Class IIa device).

Control (sham RIC): Identical protocol with bilateral upper-arm cuffs inflated to 50 mmHg (sub-diastolic pressure; no limb ischaemia induced).

Randomisation

Web-based 1:1 allocation, performed immediately after consent. Stratified by thrombolysis use. Minimisation factors: age (<70 / ≥70 years), sex, time from onset to randomisation (≤24 / >24 hours), (<10 / ≥10), systolic BP (≤170 / >170 mmHg), mechanical thrombectomy (yes/no).

Primary outcome

Functional outcome at day 90 (± 7 days): ordinal shift analysis of the modified Rankin Scale (mRS 0–6),^{8,23} assessed by central blinded telephone follow-up using the validated simplified mRS questionnaire.

Secondary outcomes

Cerebrovascular events (composite and individual components); mRS dichotomised (0–3 vs 4–6); MACCE; acute kidney injury; Barthel Index; Functional Oral Intake Scale (FOIS); cognition (TICS-M); mood (Zung Depression Scale); frailty (Clinical Frailty Scale); quality of life (EQ-5D-5L and VAS); home-time; NIHSS at day 2 and end of treatment; all-cause

mortality; neurological deterioration. Compliance and persistence analyses are reported separately (Section 6).

Early stopping

The trial was halted prior to reaching its target sample size of 1300 participants, having recruited 272 participants across 27 NHS sites. The trial steering committee, sponsor and funder approved early closure. The DMC conducted biannual safety reviews; no stopping recommendation based on efficacy or harm was made. A conditional power calculation will be presented alongside primary results to contextualise the achieved sample size.

3. Analysis Populations

Table A. Analysis populations for RECAST-3.

Population	Definition	Primary use
Safety population	All randomised participants.	Baseline descriptive statistics; all safety and compliance summaries.
Modified Intention-to-treat (mITT)	All randomised participants who received at least one dose of study treatment and have the mRS recorded at day 90.	Primary efficacy analysis; all secondary outcome analyses.
ITT	All randomised participants; missing mRS at day 90 was imputed	Pre-specified sensitivity analysis for the primary outcome only.
Per-protocol (PP)	ITT population excluding: (a) participants with a final clinical diagnosis other than acute ischaemic stroke (stroke mimic); (b) participants with any major protocol violation judged to materially affect the primary outcome.	Pre-specified sensitivity analysis for the primary outcome only.

ITT: intention-to-treat; mITT: modified ITT; PP: per-protocol. The per-protocol population will be defined at a blinded review meeting attended by the trial statistician, chief investigator, and trial manager, before database lock.

Stroke mimic definition: A participant will be classified as a stroke mimic if the final clinical diagnosis at discharge or latest clinical review is not acute ischaemic stroke — including transient ischaemic attack without DWI lesion, functional neurological disorder, metabolic encephalopathy, or other non-vascular cause. Classification is recorded by the local treating clinician on the case report form.

Major protocol violations: Defined in the trial protocol (version 6.0, see trial website for latest and superseded versions: <https://stroke.nottingham.ac.uk/recast-3/docs/public.php>). Examples include: randomisation >48 hours from onset; baseline spontaneous intracerebral haemorrhage; NIHSS <4 or >25 at randomisation; failure to obtain appropriate consent prior to randomisation.

4. Statistical Principles

Significance level and reporting

Primary outcome: Two-sided $\alpha = 0.05$. The result will be reported as an adjusted common odds ratio (acOR) with 95% confidence interval and p-value.

Secondary outcomes: No hypothesis tests will be conducted for secondary outcomes. Effect estimates (odds ratios, hazard ratios, mean differences, as appropriate) will be reported with 95% confidence intervals only. This pre-specified approach reflects the underpowered sample

size and avoids the generation of spurious significant findings. The 95% CI allows readers to assess the precision and clinical plausibility of treatment effects.

Subgroup interaction tests: Interaction p-values for the pre-specified subgroup analyses of the primary outcome will be calculated and reported but interpreted cautiously given limited power for interaction detection.

Safety analyses: Descriptive; no formal hypothesis testing. Proportions and 95% CIs will be reported by treatment arm.

Software

All analyses will be conducted in SAS (version 9.4, Institute Incorporation, Cary, North Carolina). All analysis code will be documented in a reproducible script and archived alongside the trial dataset.). All analysis code will be documented in a reproducible script and archived alongside the trial dataset.

Covariate adjustment

The primary analysis and all pre-specified secondary efficacy analyses include covariate adjustment.¹⁸ Covariates were selected a priori based on known prognostic importance and their role as minimisation variables. The covariate list is presented in Table B.

Table B. Covariates included in the primary and secondary analysis models.

Covariate	Categories / values	Rationale
Treatment allocation (RIC vs sham)	Fixed binary predictor	Primary exposure of interest
Age	Continuous variable (minimisation variable)	Strong independent predictor of stroke outcome
Sex	Male / female (minimisation variable)	Minimisation variable; sex differences in stroke prognosis
Time from onset to randomisation	Continuous variable (minimisation variable)	Earlier treatment may confer greater benefit; used to stratify analyses
Stroke severity — NIHSS	Continuous variable (minimisation variable)	Strongest single predictor of 90-day mRS
Systolic blood pressure at randomisation	Continuous variable (minimisation variable)	Elevated BP at presentation independently predicts worse outcome
Thrombolysis (IVT) received	Yes / no (stratification factor)	IVT changes the reperfusion context and expected RIC interaction
Mechanical thrombectomy (MT) received	Yes / no (minimisation variable)	EVT patients have the greatest reperfusion injury burden
Pre-morbid mRS	0 / 1 / 2 / 3 (additional prognostic covariate)	Reflects baseline functional reserve and strong independent predictor of stroke outcome
Recruiting centre	Fixed effect	Accounts for between-site heterogeneity in case-mix and practice

IRI: ischaemia-reperfusion injury; IVT: intravenous thrombolysis; EVT: endovascular thrombectomy; mRS: modified Rankin Scale; BP: blood pressure; NIHSS: National Institutes of Health Stroke Scale.

5. Primary Analysis

Outcome definition

The primary outcome is the modified Rankin Scale (mRS) at day 90 (± 7 days), assessed as a 7-level ordinal scale from 0 (no symptoms) to 6 (death). The mRS is administered by the national coordinating centre using the validated telephone simplified mRS questionnaire,⁹ blinded to treatment allocation.

Statistical method

The primary analysis uses an ordinal logistic regression (OLR) model — a proportional odds model — fitting the 7-level mRS as the outcome.²³ The treatment effect is expressed as an adjusted common odds ratio (acOR): an acOR < 1 (odds of a poor outcome) indicates a shift towards lower (better) mRS scores in the RIC arm relative to sham.

Test of the proportional odds assumption

Before fitting the proportional odds model, the assumption of proportionality will be tested using the likelihood test and reported. If the assumption is violated (likelihood test $p < 0.05$), a partial proportional odds model (generalised ordered logistic regression) will be used as the primary analysis, and the standard proportional odds result will be reported as a sensitivity analysis.

Presenting the mRS distribution

The mRS distribution at day 90 by treatment arm will be displayed as a horizontal stacked bar chart, showing proportions at each mRS level (0, 1, 2, 3, 4, 5, 6) with the treatment arms arranged one above the other. Cumulative proportions at key thresholds (mRS 0–1, 0–2, 0–3) will be tabulated alongside the ordinal analysis.

Handling of missing primary outcome data

The primary analysis will use complete cases (participants with observed mRS at day 90 or confirmed death). Missing primary outcome data will be reported by treatment arm. If the proportion missing in either arm exceeds 5%, multiple imputation will be used as the primary sensitivity analysis ²⁴ (see Section 9).

6. Secondary Analyses

Reporting convention: All secondary analyses are pre-specified and descriptive in nature. Effect estimates will be reported with 95% confidence intervals only. No p-values will be calculated or reported for secondary outcomes. This applies consistently across all secondary efficacy and patient-reported outcomes. Readers should interpret the CIs in terms of the range of treatment effects compatible with the data, not as a basis for significance testing.

Covariates: All secondary analyses use the same covariate set as the primary analysis (Table B), applied to the appropriate regression model for the outcome type.

Table C. Secondary outcomes: data types, statistical methods, and effect measures reported.

Outcome	Data type	Statistical method	Effect measure reported	Timepoint
Cerebrovascular events (composite)	Time-to-first-event	Cox proportional hazards regression, adjusted for covariates	HR (95% CI)	Day 90
Individual components of cerebrovascular composite	Binary (yes/no per component)	Logistic regression, adjusted for covariates	OR (95% CI)	Day 90
mRS dichotomised (0–3 vs 4–6)	Binary	Logistic regression, adjusted for covariates	OR (95% CI)	Day 90
MACCE composite (CV death, MI, all stroke)	Time-to-first-event	Cox proportional hazards regression, adjusted for covariates	HR (95% CI)	Day 90
Acute kidney injury — any	Binary	Logistic regression, adjusted for covariates	OR (95% CI)	During admission
Barthel Index	Continuous (0–100)	Multiple linear regression, adjusted for covariates	Mean difference (95% CI)	Day 90
Functional Oral Intake Scale (FOIS)	Ordinal (1–7)	Ordinal logistic regression, adjusted for covariates	Common OR (95% CI)	Day 90
TICS-M (cognition)	Continuous	Multiple linear regression, adjusted for covariates + baseline NIHSS	Mean difference (95% CI)	Day 90
Zung Depression Scale (continuous)	Continuous	Multiple linear regression, adjusted for covariates	Mean difference (95% CI)	Day 90
Clinical Frailty Scale (CFS)	Ordinal (1–9)	Ordinal logistic regression, adjusted for covariates	Common OR (95% CI)	Day 90
EQ-5D-5L utility index	Continuous	Multiple linear regression, adjusted for covariates	Mean difference (95% CI)	Day 90
EQ-5D-5L visual analogue scale (VAS)	Continuous (0–100)	Multiple linear regression, adjusted for covariates	Mean difference (95% CI)	Day 90
Home-time (days at home 0–90)	Continuous	Multiple linear regression;	Mean difference (95% CI)	Day 0–90
NIHSS (change from baseline)	Continuous	Multiple linear regression, adjusted for covariates + baseline NIHSS	Mean difference (95% CI)	Day 2 and end of treatment

All effect measures are accompanied by 95% CI only (no p-values). HR: hazard ratio; OR: odds ratio; CI: confidence interval; FOIS: Functional Oral Intake Scale; TICS-M: Telephone Interview for Cognitive Status modified; CFS: Clinical Frailty Scale; EQ-5D-5L: EuroQOL 5-dimension 5-level; VAS: visual analogue scale; MACCE: major adverse cardiac and cerebrovascular events; NIHSS: National Institutes of Health Stroke Scale; KDIGO: Kidney Disease Improving Global Outcomes.

Notes on specific secondary outcomes

Cerebrovascular events composite

The composite of cerebrovascular events comprises: (i) symptomatic intracranial haemorrhage; (ii) symptomatic swelling of the original infarct; (iii) extension of ischaemic stroke (within 72 hours of randomisation); (iv) recurrent ischaemic stroke (after 72 hours, same or different territory); (v) recurrent stroke of unknown type; and (vi) neurological deterioration (NIHSS increase ≥ 4 points or GCS drop ≥ 2 points from baseline, not attributable to other causes). All events will be centrally and blindly adjudicated before analysis.

mRS dichotomised

The mRS will be dichotomised as 0–3 (independent) versus 4–6 (dependent or dead). This is analysed as a binary outcome using logistic regression with covariate adjustment. Typically, a dichotomy is chosen at 0-2 / 3-6. However, trial inclusion criteria allowed a baseline mRS range 0-3, hence this choice.

MACCE

MACCE is defined as the composite of: cardiovascular death; myocardial infarction (NSTEMI or STEMI by universal definition); and all stroke (ischaemic, haemorrhagic, or unknown type). Time-to-first-MACCE event will be analysed using Cox regression. Individual components will be analysed as binary outcomes by logistic regression.

Acute kidney injury

AKI is classified by KDIGO 2012 criteria using creatinine measurements obtained during the hospital admission. AKI will be analysed as binary (any AKI versus none) by logistic regression.

Home-time

Home-time is defined as the number of days between hospital discharge and day 90 spent at the participant's usual place of residence (home or usual care home). Days in hospital, rehabilitation unit, or new institutional care are excluded. Home-time ranges from 0 (never discharged home or died) to 90. It will be analysed as a continuous outcome by multiple linear regression.

NIHSS at day 2 and end of treatment

NIHSS is assessed by local investigators at day 2 and at end of treatment (or discharge if earlier). These assessors are not blinded to treatment allocation; results should therefore be interpreted with additional caution and treated as supportive only.

Compliance Analyses

Overview: Compliance and persistence analyses are descriptive and are conducted on the safety population (all randomised participants), reported separately from efficacy secondary outcomes. Results are presented by treatment arm; exact 95% CIs will be reported for proportions. The main paper will report on initiation, implementation and reasons for reduced compliance.

Initiation

The proportion of participants receiving at least one dose of allocated treatment will be reported with 95% CI. Participants who did not receive any dose will be listed with reasons and excluded from the ITT population (as defined in Section 3) but retained in the safety population.

Implementation: doses expected and received

For the overall treatment period, the following will be reported:

- Doses expected (accounting for abbreviated treatment due to early discharge or transfer): median [IQR] and mean (SD)
- Doses received: median [IQR] and mean (SD)
- Proportion of expected doses received (all participants): mean (SD)

Participants for whom 28 doses were expected: Mean (SD) proportion of doses received; n (%) receiving ≥80%, 50–79%, and <50% of expected doses.

Participants for whom <28 doses were expected: Mean (SD) proportion of doses received; n (%) receiving ≥80%, 50–79%, and <50% of expected doses. An abbreviated course is protocol-compliant when discharge or transfer to a non-participating site occurs before day 14, provided ≥2 doses have been received.

Reasons for reduced compliance

Among participants who did not receive all expected doses, the following reasons will be tabulated (participants may have more than one reason):

- Intolerance to cuff pressure
- Refusal not due to intolerance
- Medically unwell
- SAE or serious adverse device event (SADE)
- Reduced dose administered to aid compliance
- Other reason

Discontinuation

Among participants who did not complete all expected doses, reasons for early discontinuation will be tabulated:

- Transfer or discharge to a non-participating site (protocol-compliant discontinuation)
- Participant withdrawn from treatment but remains under trial follow-up for outcomes
- Participant alive and withdrawn but permitting data collection from medical records
- Participant withdrawn from the trial entirely
- Death before completing the treatment course

Further adherence analyses will form a secondary paper and will also include the following

Adherence

For each of the 28 possible doses, the following will be reported by treatment arm:

- Mean (SD) total cuff inflation time (minutes, out of a target 20 minutes per dose) and total cuff inflation time
- Proportion completing >90%, 50–90%, and ≤50% of expected inflation time
- Proportion using bilateral versus single-limb delivery
- Proportion using automated versus manual device delivery
- Mean (SD) total time from intervention start to finish (minutes) (i.e. sum of inflation time)

Weekend treatment

The proportion of participants who received RIC/sham on all weekends, some weekends, or no weekends during their treatment period will be reported by treatment arm.

Persistence

Persistence captures the number of days on which at least one dose was received, as distinct from the total number of doses. The following will be reported:

- Days expected to receive RIC/sham: mean (SD) and median [IQR]
- Days receiving at least one dose: mean (SD) and median [IQR]
- Proportion of expected days on which treatment was received: mean (SD)

- Proportion receiving treatment on all 14 scheduled treatment days (full persisters): n (%)
- For participants with 28 doses expected: mean (SD) and median [IQR] days received
- For participants with abbreviated course: mean (SD) and median [IQR] days received

Patient-reported outcomes

All patient-reported outcomes at day 90 are collected by the central coordinating centre through blinded telephone interview. Where a participant cannot complete the interview, a proxy response from a consultee is accepted for mRS and EQ-5D-5L. For TICS-M, only direct participant responses will be used; proxy cognitive assessments will not be substituted.

7. Pre-specified Subgroup Analyses

Pre-specified subgroup analyses will be conducted for the primary outcome (mRS ordinal shift) only. Each subgroup is examined by including a treatment-by-subgroup interaction term in the primary OLR model. Results are presented as the adjusted cOR (95% CI) within each subgroup, together with the interaction p-value. The forest plot will display subgroup ORs and 95% CIs.

With n=272, the trial has limited power to detect interaction effects. Interaction p-values are therefore presented for completeness. The pre-specified subgroups are listed in Table D.

Table D. Pre-specified subgroup analyses for the primary outcome.

Subgroup	Categories	Scientific rationale
Age	<70 years vs ≥70 years	Minimisation variable; older patients may have attenuated RIC response
Sex	Male vs female	Minimisation variable; preclinical sex differences in RIC efficacy reported
Time to randomisation	≤24 hours vs >24 hours	Earlier RIC application may produce greater neuroprotective benefit
Stroke severity (NIHSS)	< 0 / 10–20 / >20	Minimisation variable; more severe strokes have greater IRI burden
Systolic BP at randomisation	≤170 mmHg vs >170 mmHg	Minimisation variable; elevated BP may reflect different physiology
Thrombolysis (IVT) received	Yes vs no	IVT may modulate RIC benefit
Mechanical thrombectomy (MT) received	Yes vs no	EVT may modulate RIC benefit
Diabetes mellitus	Yes vs no	Diabetes recognised to attenuate RIC effects; important biological interaction
Pre-morbid frailty (CFS)	None/mild (1–3) vs moderate/severe (4–9)	Frailty associated with differential treatment response in acute stroke trials
Vascular territory	Anterior vs posterior circulation	Different haemodynamic and collateral characteristics between territories
Stroke aetiology	Large vessel / cardioembolic vs small vessel / other	Aetiology influences reperfusion injury magnitude and likely RIC response
Atrial fibrillation	Yes vs no	AF-related strokes tend to be larger, with greater expected reperfusion injury. Prior studies suggest potential interaction in AF.

All subgroup analyses include a treatment × subgroup interaction term in the primary OLR model. Results are displayed as a forest plot showing adjusted OR (95% CI) within each stratum and the interaction p-value. NIHSS: National Institutes of Health Stroke Scale; BP: blood pressure; CFS: Clinical Frailty Scale; IVT: intravenous thrombolysis; EVT: endovascular thrombectomy; RIC: remote ischaemic conditioning.

8. Safety Analyses

Overview

Safety analyses are conducted on the safety population (all randomised participants). Safety data are summarised descriptively. Given the early stopping and reduced sample size, formal hypothesis testing is not appropriate for safety endpoints; proportions and 95% CIs will be reported by treatment arm. Absolute risk differences and 95% CIs will be presented for the most clinically important endpoints.

Table E. Safety endpoints and statistical approach.

Safety endpoint	Data type	Statistical approach	Timepoint
All-cause mortality	Time-to-event	Cox regression; HR (95% CI)	Day 90
Neurological deterioration due to any cause (NIHSS increase by ≥4 or GCS decrease by ≥2)	Binary	Proportion (%); logistic regression; OR (95% CI)	Day 2
Neurological deterioration due to any cause (NIHSS increase by ≥4 or GCS decrease by ≥2)	Binary	Proportion (%); logistic regression; OR (95% CI)	End of treatment
Symptomatic intracranial haemorrhage	Binary	Proportion (%); logistic regression; OR (95% CI)	Day 2 and day 90
Symptomatic infarct swelling	Binary	Proportion (%); logistic regression; OR (95% CI)	Day 2 and day 90
Symptomatic haemorrhagic transformation	Binary	Proportion (%); logistic regression; OR (95% CI)	Clinically reported
Systemic embolism	Binary	Proportion (%); logistic regression; OR (95% CI)	Day 90
Neurovascular limb compromise	Binary	Proportion (%); logistic regression; OR (95% CI)	End of treatment
Related Adverse device events that stopped treatment (e.g. skin petechiae, bruising)	Binary	Proportion (%) by type; no formal test	End of treatment
Serious adverse events (not inclusive of SAEs, ≤ 28 days)	Count and binary	Proportions (%); tabulated by arm; no formal test	≤ 28 days
Systolic BP change	Continuous (repeated)	Linear mixed-effects model; time × treatment interaction	Each dose

OR: odds ratio; HR: hazard ratio; CI: confidence interval; BP: blood pressure. No p-values are reported for safety endpoints.

SAE reporting window

All SAEs are collected within 28 days of randomisation. After 28 days, only fatal SAEs and the pre-specified safety outcome events (death, stroke, TIA, intracranial haemorrhage, systemic embolism, neurovascular limb compromise) are collected to day 90. SAEs will be tabulated by system organ class.

Adverse device events

Adverse events judged by local investigators to be related to the RIC or sham device (including skin petechiae, bruising, discomfort, or any event requiring device discontinuation) will be listed individually and tabulated by type and arm. No formal statistical comparison will be made; proportions and exact 95% CIs will be reported.

Imaging

An originally planned sub study of those undergoing MT with CT perfusion was abandoned due to low recruitment. Routinely performed imaging as standard of care is collected but will take longer to collate and analyse, and will be reported separately to the main paper. Haemorrhagic transformation (HT) will be classified using the Heidelberg Bleeding Classification on all available post-randomisation CT scans,²⁵ read by a central neuroradiologist blinded to treatment allocation.

Blood pressure monitoring

Several prior trials have reported on the safety of RIC and these analyses will be reported separately (i.e. not in the main paper). Systolic and diastolic blood pressure are recorded before and after each dose of RIC or sham. Change in systolic BP from pre-dose to post-dose will be analysed using a linear mixed-effects model. This will be reported in a secondary paper.

9. Sensitivity and Supplementary Analyses

Multiple imputation for missing primary outcome

If missing primary outcome data appear informative (> 5% missing in either arm), multiple imputation by chained equations (MICE, using PROC MI in SAS) will be used as the primary sensitivity analysis for the primary outcome.²⁴ At least 20 imputed datasets will be generated. The imputation model will include: mRS at day 90 (imputed), age, sex, time to randomisation, NIHSS, SBP, thrombolysis, thrombectomy, pre-morbid mRS, diabetes, and treatment allocation. The primary OLR model will be run on each imputed dataset and results combined using Rubin's rules. Results of the imputed analysis will be compared with the complete-case analysis; if they differ substantially, the reasons will be explored and reported.

Worst-case and best-case extreme sensitivity analyses for the primary outcome

Two extreme-case analyses will be performed if missing primary outcome data exceed 5% in either arm:

Worst case for RIC: Participants with missing mRS in the RIC arm assigned mRS = 6; those missing in the sham arm assigned mRS = 0.

Best case for RIC: Participants with missing mRS in the RIC arm assigned mRS = 0; those missing in the sham arm assigned mRS = 6.

These analyses define the range within which the true treatment effect must lie, regardless of the missing data mechanism.

Per-protocol sensitivity analysis

The primary OLR model will be re-run in the per-protocol population (Section 3), excluding stroke mimics and participants with major protocol violations.

Unadjusted analysis

An unadjusted ordinal logistic regression (treatment arm only, no covariates, no centre effect) will be reported alongside the primary adjusted analysis. The comparison between adjusted and unadjusted results illustrates the contribution of covariate adjustment to precision.

Conditional power calculation

Given the trial closed at $n = 272$ (21% of the planned sample), the conditional power will be estimated: given the observed treatment effect (log-cOR) and its standard error at $n=272$, the probability of achieving a statistically significant primary outcome (two-sided $p < 0.05$) had the trial continued to $n=1300$ will be calculated. This assumes the true treatment effect equals the observed effect at the interim sample size. This calculation will be reported alongside the primary result to contextualise its interpretation.

10. Baseline Characteristics

Baseline characteristics will be reported for the safety population (all randomised participants), overall and by treatment arm, without formal statistical comparison (p-values or hypothesis tests). Randomisation ensures expectation of balance; statistical testing of baseline differences is uninformative and not recommended by CONSORT guidelines.²⁶

Continuous variables will be summarised as mean (SD) if approximately normally distributed, or median (IQR) if skewed (based on Shapiro-Wilk test and visual inspection). Categorical variables will be reported as n (%). Any notable imbalance — defined as a standardised mean difference (SMD) > 0.10 — will be discussed in the results paper.

Table F. Baseline variables to be reported by treatment arm.

Variable	Summary statistic	Data type
Age (years)	Mean (SD)	Continuous
Sex (male)	n (%)	Binary
Ethnicity	n (%) by category	Categorical
NIHSS at randomisation	Median (IQR)	Ordinal
Pre-morbid mRS (0 / 1 / 2 / 3)	Median (IQR)	Ordinal
Pre-morbid Clinical Frailty Scale	Median (IQR)	Ordinal
Time from onset to randomisation (h)	Median (IQR)	Continuous
Time category (0–24 h vs > 24–48 h)	n (%)	Binary
Systolic blood pressure (mmHg)	Mean (SD)	Continuous
Diastolic blood pressure (mmHg)	Mean (SD)	Continuous
Blood glucose (mmol/L)	Median (IQR)	Continuous
Temperature (°C)	Mean (SD)	Continuous
Atrial fibrillation	n (%)	Binary
Hypertension	n (%)	Binary
Diabetes mellitus	n (%)	Binary
Prior stroke or TIA	n (%)	Binary
Ischaemic heart disease	n (%)	Binary

Variable	Summary statistic	Data type
Current smoker	n (%)	Binary
Thrombolysis (IVT) received	n (%)	Binary
Mechanical thrombectomy received	n (%)	Binary
Stroke territory (anterior vs posterior)	n (%)	Binary
Stroke classification (TOAST criteria)	n (%)	Nominal
Time from onset to first RIC/sham dose (h)	Median (IQR)	Continuous

All variables reported overall and by treatment arm (RIC and sham). No p-values for baseline comparisons. NIHSS: National Institutes of Health Stroke Scale; mRS: modified Rankin Scale; CFS: Clinical Frailty Scale; IQR: interquartile range; SD: standard deviation; TOAST: Trial of Org 10172 in Acute Stroke Treatment; TIA: transient ischaemic attack.

11. Reporting Standards

The primary results paper will be reported in accordance with CONSORT guidelines for parallel-group randomised trials.²⁶ A completed CONSORT checklist will be submitted as a supplementary file alongside the manuscript.

Given the early closure of RECAST-3, the results paper will explicitly:

- State the planned (n=1300) and achieved (n=272) sample sizes, and the reasons for early closure
- Provide a conditional power calculation at the achieved sample size
- Acknowledge that all secondary analyses are underpowered and descriptive
- Avoid using the word "significant" in relation to secondary outcomes
- Present the primary outcome result with full inferential statistics (cOR, 95% CI, p-value), and all secondary outcomes with effect estimates and 95% CIs only
- Contextualise the RECAST-3 findings within the growing international evidence base, including a meta-analytic summary where possible
- Refrain from drawing definitive conclusions about RIC efficacy solely based on RECAST-3 data