MAnagement of Systolic blood pressure during Thrombectomy by Endovascular Route for acute ischaemic STROKE randomized clinical trial: the MASTERSTROKE trial

Statistical Analysis Plan
Version 1.1
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An international randomised clinical trial endorsed by the Australian and New Zealand College of Anaesthetists Clinical Trials Network (ANZCA-CTN)

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Contents

0. Abbreviations

Abbreviation	*Full title*
ASPECTS	Alberta Stroke Program Early CT Score
BP	Blood pressure
CBF	Cerebral blood flow
CI	Confidence interval
CONSORT	Consolidated Standards of Reporting Trials
CT	Computed Tomography
CTA	Computed Tomography Angiography
DSMB	Data Safety Monitoring Board
EVT	Endovascular thrombectomy
GA	General anaesthesia
ICA	Internal carotid artery
IH	Induced hypertension
IQR	Interquartile range
ITT	Intention to treat
LVO	Large vessel occlusion
MASTERSTROKE	MAnagement of Systolic blood pressure during Thrombectomy by Endovascular Route for acute ischaemic STROKE
MCA	Middle cerebral artery
MRI	Magnetic Resonance Imaging
mRS	Modified Rankin Scale
mTICI	Modified Treatment In Cerebral Infarction
NIHSS	National Institute of Health Stroke Scale
OR	Odds ratio
PP	Per protocol
RCT	Randomised controlled trial
SAP	Statistical analysis plan
SBP	Systolic blood pressure
sICH	Symptomatic intracranial haemorrhage
SITS-MOST	Safe Implementation of Thrombolysis in Stroke-Monitoring Study

1. Administrative information

1.1 Study identifiers

Protocol Version: 1.4 Dated 8th August 2024

ClinicalTrials.gov NCT05645861
Australian New Zealand Clinical Trials Registry: ACTRN12619001274167p

1.2 Revision history

Version	Date	Details
1.0 draft	8th September 2025	D Campbell
1.1 final	17th November 2025	DC, AB, CF, WD

1.3 Contributors to the statistical analysis plan

1.3.1 Roles and responsibilities

Name	Role	Affiliation	Contribution to SAP
Dr Doug Campbell	Principal Investigator	Dept of Anaesthesia, Auckland City Hospital, New Zealand	Wrote first draft v1.0 and edited all revisions
Prof Alan Barber	Senior Investigator	Dept of Neurology, Auckland City Hospital, New Zealand	Edited version v1.0
Dr William Diprose	Co-investigator	Dept of Neurology, John Hunter Hospital, NSW, Australia	Edited version v1.0
Prof Chris Frampton	Trial Statistician	Dept of Medicine, University of Otago, Christchurch, New Zealand	Edited version v1.0

1.3.2 Approvals

We have reviewed this statistical analysis plan and consider it the final version and is written in accordance with to the protocol. It is compliant with the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) E9 Statistical Principles for Clinical Trials. It adheres to Guidelines for the Content of Statistical Analysis Plans in Clinical Trials. [1]

2. Introduction

2.1 Study synopsis

The MASTERSTROKE trial is prospective, randomised clinical trial of two systolic blood pressure targets during general anaesthesia for endovascular thrombectomy for anterior circulation ischaemic stroke and subsequent functional recovery.

2.2 Rationale

The effectiveness of endovascular thrombectomy (EVT) for the treatment of large vessel occlusion (LVO) ischaemic stroke has been demonstrated in multiple randomized controlled trials (RCT). However, peri-procedural factors such as relative intra-procedural hypotension have been shown to worsen outcomes. Cerebral autoregulation, a protective mechanism preserving cerebral blood flow (CBF) over a wide range of systemic blood pressure (BP), is impaired after ischaemic stroke. Common anaesthetic agents such as sevoflurane and propofol used as part of general anaesthesia (GA) for EVT, also impair cerebral autoregulation in a dose-dependent fashion. Consequently, global and regional CBF in ischaemic territories of the brain become BP-dependent during GA, thus collateral blood flow to the ischaemic penumbra may be decreased by relative hypotension and increased by induced hypertension.

A major therapeutic goal in the acute management of LVO stroke is to protect the ischaemic penumbra until restoration of blood flow. Induced hypertension (IH) has the potential to increase penumbral CBF via leptomeningeal and collaterals vessels. Other methods to augment blood flow to the ischaemic territory have been suggested including colloid infusions, inhaled nitric oxide, intra-aortic balloon counter-pulsation and sphenopalatine ganglion stimulation. Some of these methods are complex to incorporate into acute stroke care whereas IH administered by expert anaesthesiologists during GA for EVT is simple and physiologically plausible.

Induced hypertension, or BP augmentation, has the theoretical potential to increase procedural complications such as groin haematoma and symptomatic intracranial haemorrhage, as well as reperfusion injury and cerebral oedema. These harms can be mitigated by delivering IH until recanalization has been achieved, and then targeting lower BP as per usual clinical care. The potential for therapeutic benefit from an augmented BP management regimen and the possibility of additional harm demonstrates that there is clinical equipoise that can only be resolved by performing a large RCT with efficacy and adverse outcomes testing for overall effectiveness. We aim to test the overall effectiveness, of an augmented SBP management target (170 mmHg) in comparison to the current standard practice (140 mmHg) during GA for EVT, by assessing functional recovery as measured by mRS score at 90 days.

A more extensive rationale can be found in the published rationale and protocol. [2]

2.3 Objectives

To test whether an SBP target of 170 mmHg during GA for EVT will lead to superior functional recovery at 3 months compared to an SBP target of 140 mmHg in patients with acute anterior circulation LVO stroke.

Primary endpoint

mRS assessed at 3 months

Secondary objectives

To test functional independence at 90 days (mRS 0, 1 and 2) comparing an SBP target of 140 mmHg or 170 mm Hg in patients with acute anterior circulation LVO stroke.

To test excellent functional recovery at 90 days (mRS 0 or 1) comparing an SBP target of 140 mmHg or 170 mm Hg in patients with acute anterior circulation LVO stroke.

To test patient days at home within 90 days (which are the number of days a participant resides at home or their previous domicile in the first 90 days post-stroke) comparing an SBP target of 140 mmHg or 170 mm Hg in patients with acute anterior circulation LVO stroke

Secondary endpoints

Functional independence, as defined by mRS of 0, 1 or 2 at 90 days.

Excellent functional outcome, as measured by mRS of 0, or 1 at 90 days.

Home days (days alive at home) which are the number of days a participant resides at home or their previous domicile in the first 90 days post-stroke.

Safety Objectives

To test all-cause mortality by 90 days comparing an SBP target of 140 mmHg or 170 mm Hg in patients with acute anterior circulation LVO stroke.

To test incidence of symptomatic intracranial haemorrhage (sICH) as defined by the Safe Implementation of Thrombolysis in Stroke-Monitoring Study (SITS-MOST) definition as a Type 2 parenchymal haemorrhage with deterioration in NIHSS score of 4 points or death within 36 hours, comparing an SBP target of 140 mmHg or 170 mm Hg in patients with acute anterior circulation LVO stroke.

To test incidence of a composite outcome of intra-procedural complications (including target vessel dissection or perforation, intracranial haemorrhage and groin haematoma), comparing an SBP target of 140 mmHg or 170 mm Hg in patients with acute anterior circulation LVO stroke.

Safety endpoints

Symptomatic intracranial haemorrhage (sICH) as defined by the SITS-MOST definition as a Type 2 parenchymal haemorrhage with deterioration in NIHSS score of 4 points or death within 36 hours.

All-cause mortality up to 90 days.

Composite outcome of intra-procedural complications (including target vessel dissection or perforation, intracranial haemorrhage and groin haematoma). Intra-procedural definitions are described in the Manual of Operations version 1.2, date 8th August 2024.

3. Study methods

3.1 Trial design

Prospective, randomized, parallel group, open label, multicentre clinical trial with blinded assessment of outcomes.

3.2 Treatment allocation

Participants are randomised in a 1:1 ratio to a SBP target of 140 mm Hg or a SBP target of 170 mm Hg with randomisation by centre in permuted blocks of eight and will occur after most inclusion and exclusion criteria have been evaluated.

3.3 Sample size calculation

A more extensive sample size justification can be found in the published rationale and protocol. [2] In brief, simulations were run using relevant national mRS data to determine the sample size required for the comparison of the primary outcome of 90-day mRS between the two treatment groups. A minimum favourable shift in the 90-day mRS would equate to approximately one third of participants within each response category (0-6) showing lower mRS. Simulations using this scenario and comparing groups using the Mann-Whitney U test, demonstrated that 550 participants (275 per group) provide 90% power to detect this difference in mRS outcome scores as statistically significant (2-tailed α=0.05). This improved shift in scores between the two groups equates to differences in the mean mRS of approximately 0.5 and an improvement in the proportion with an independent outcome (mRS 0-2) from approximately 58% to 68%, a clinically important treatment effect of 10%.

3.4 Framework

All hypothesis testing in this trial will use an equivalence hypothesis testing framework.

3.5 Interim analysis

Interim analysis for safety was performed after 300 complete outcome assessments. Interim analysis for safety allowed the Steering Committee to review the safety measures and to consider stopping the trial early if safety concerns were reported by the DSMB. No safety concerns were reported to the Steering Committee and the trial is planned to continue to completion. No protocol changes were made consequent to the interim analysis

3.6 Timing of final analysis

Final analysis will be after 90 day follow up is complete and database locked.

3.7 Timing of outcome assessments

All primary and secondary outcomes are assessed at 3 months, except two safety outcomes (procedural complications and sICH) which are assessed up to 36 hours post-procedure.

4. Statistical principles

The baseline characteristics of participants will be presented by allocated group. This will include demographic, and clinical information collected at recruitment, and further defined after relevant investigations. Discrete variables will be summarized by frequencies and percentages. Continuous variables will be summarized by mean and SD, or median and IQR as appropriate.

4.1 Baseline characteristics

Baseline demographic and clinical characteristics presented will include the following variables

- Age
- Sex
- Ethnicity
- Time from stroke onset (0-6 hours, 6 to 24 hours, wake up stroke)
- Admission NIHSS score
- Use of thrombolytic agent
- Target vessel occlusion (ICA, M1 or M2 middle cerebral artery)
- Treated hypertension
- Atrial fibrillation
- Diabetes
- Smoking
- Baseline SBP
- Glucose
- Temperature
- ASPECTS (0-5, 6-8, 9-10)

These data will be examined for any imbalances between randomised treatments. No formal hypothesis testing will be conducted on these baseline variables.

Interventional radiology and anaesthesia process of care will include the following variables evaluated during the procedure

- Procedure duration
- Maintenance anaesthetic agent (drug choice, dose, concentration)
- mTICI score
- median SBP (reported to assess adherence to intervention)
- median ETCO2
- median SpO2
- median vasopressor use
- median fluid volume
- disposition (PACU/ICU)

These data will be examined for any imbalances between randomised treatments. No formal hypothesis testing will be conducted on these baseline variables.

4.2 Confidence intervals and P-values

We will report two-sided results and use a P value <0.05 as a measure of statistical significance. There will be no adjustment for multiplicity where there are multiple comparisons. Where confidence levels are presented, the 95% confidence interval will be reported.

4.3 Adherence and protocol deviations

A participant is considered adherent to the intervention if median procedural SBP (from GA induction until reperfusion (or timing of TICI assessment if unsuccessful), is within 10 mm Hg of allocated SBP eg 130-150 mm Hg for 140 mm Hg group, 160-180 mm Hg for 170 mm Hg group. The intervention adherence as measured for each participant by the median procedural SBP, will be summarised as the median SBP and IQR from GA induction to reperfusion by randomised group. This data will be presented as a box and whisker plot and the frequency and percentage considered adherent generated. Non-adherence and other protocol deviations will be presented as frequency and percentage.

4.4 Analysis populations

4.4.1 Intention to treat population

The ITT population will include all randomized patients who had GA for EVT, regardless of whether they received the allocated treatment and satisfied entry criteria. The ITT population will be used to evaluate primary and secondary efficacy outcomes and the safety outcomes. Participants within the ITT population will be analysed in the group to which they were randomised irrespective of the actual treatment received.

4.4.2 Per protocol population

The PP population will include all ITT participants without significant protocol violations. Significant protocol violations include non-adherence to allocated treatment (as defined above) and not satisfying all entry criteria, will be listed by reason on the CONSORT participant flow diagram when defining the PP population. The PP analysis will be considered a secondary analysis to the primary ITT analysis and will evaluate primary and secondary outcomes.

4.4.3 Safety population

The safety population will include all ITT participants who had GA for EVT. Participants within the safety population will be analysed in the group defined by the actual treatment received irrespective of randomisation. The safety population will be used for sensitivity analyses of the safety endpoints including a safety analysis of the PP population.

4.4.3 Subject disposition

The flow of participants through the MASTERSTROKE trial will be displayed in a CONSORT participant flow diagram. The diagram will detail number of patients who met eligibility criteria, including the number of patients who were ultimately included and reasons for excluding participants. The numbers completing 90-day mRS assessment and lost to follow-up will be reported. The numbers of participants in the ITT and PP populations will be outlined.

5. Trial population

5.1 Screening data

Screening log data by site will be collected.

5.2 Eligibility

Adults (≥18 yr) who fulfil inclusion criteria, none of the exclusion criteria, and have undergone an appropriate consenting process.

5.2.1 Inclusion criteria

- Patients diagnosed with anterior circulation LVO stroke (ICA or proximal M1 or M2 segment of MCA) ; treated with EVT within 6 hrs of stroke onset **or** EVT patients presenting within 6-24 hours with favourable penumbra on CT perfusion scanning **or** 'wake-up' stroke
- having GA from the start of the case
- Pre-event functionally independent e.g. mRS 0-2

5.2.2 Exclusion criteria

- terminal illness with expected survival <1 year
- pregnancy
- cardiovascular conditions where BP targeting will be contra-indicated
- unable to participate in 3-month follow up
- "Rescue"' procedures eg acute ischaemic stroke associated with major medical procedures such as coronary artery stenting and coronary artery bypass

5.3 Withdrawal and follow up

The ITT population will consist of participants who have GA for EVT. Patients can withdraw from trial related follow-up at any point post-procedure. Reasons and details for withdrawal, and reasons for loss to follow-up will be recorded on the CONSORT participant flow diagram.

6. Analysis

6.1 Outcome definitions.

All outcomes will be assessed by blinded outcome assessors.

The primary outcome is mRS assessed at 90 days.

The secondary outcomes are

Home days (days alive at home) which are the number of days a participant resides at home or their previous domicile in the first 90 days post-stroke

Functional independence categorized as a mRS of 0, 1 or 2 assessed at 90 days. Excellent functional independence categorized as mRS of 0 or 1 at 90 days

The safety outcomes are

Symptomatic intracranial haemorrhage (sICH) as defined by the Safe Implementation of Thrombolysis in Stroke-Monitoring Study (SITS-MOST) definition as a Type 2 parenchymal haemorrhage with deterioration in NIHSS score of 4 points or death within 36 hours. This outcome will require adjudication by the Endpoint Adjudication Committee.

All-cause mortality will be assessed as a time to event variable.

Composite outcome of intra-procedural complications (including target vessel dissection or perforation, intracranial haemorrhage and groin haematoma) assessed up to 36 hours.

6.2 Analysis methods

The primary analysis will be conducted on the ITT population. Any missing 90-day mRS will be estimated using clinical information available to blinded assessors up to time of loss to follow up. Grading will use the Rankin Focussed Assessment rating form. The primary analysis will use the Mann-Whitney U test to analyse the shift in the distribution of the 7-category mRS from baseline to day 90. The treatment effect will be presented as an OR, with a 95% CI generated from a multinomial proportional odds regression model. There will be no covariate adjustment in the primary analysis. An initial exploration will present a histogram of mRS categories by randomised group to assess for parallelism, determine if the treatment effect is consistent across all categories and provide insight into potential violations of the proportional odds assumption. A secondary adjusted analysis will be performed on the primary outcome using a general linear model. Adjusting covariates will be prognostic factors known to be associated with outcome: age, sex, baseline mRS, baseline NIHSS [4]. A sensitivity analysis will be performed on ITT population who had mRS assessed at 90 days.

There will be a PP analysis using the PP population defined in 4.4.2.
The analysis of the dichotomous endpoints including functional independence, excellent functional recovery, sICH and the composite safety outcome will be compared using logistic

regression and summarised as odds ratios with 95% confidence intervals (CI). Unadjusted and adjusted analyses will be performed using the covariates described above.

Home days (days alive at home) will be compared between randomised groups using the non-parametric Mann-Whitney U test.

All-cause mortality at 90 days will be estimated using the Kaplan-Meier method and compared using Greenwood's standard error estimates.

All analyses of the primary, secondary and safety outcomes will also be undertaken and presented using the PP population.

Statistical analysis will be performed using SPSS v30.0.

6.3 Missing data

For missing data, we will not perform any imputation or additional processing except 90-day mRS, as described in Section 6.2. In the event that a patient withdraws (discontinues the study or is lost to follow-up) from the study, information on their survival and secondary endpoint status at the time they are withdrawn will be included in the relevant endpoint analysis. All available data will be used as appropriate to the objectives and analyses outlined in the analysis plan.

6.4 Additional analyses

There is a plausible rationale why the relative treatment effects could be different in relevant sub-groups. In particular, stroke severity (as assessed by baseline NIHSS or ASPECT score) could affect degree of cerebral autoregulation impairment. Additionally, physiological factors (SBP and ETCO2) and collateral status could all influence the relative BP treatment effects. Apriori subgroups have been identified for further exploratory analyses. Subgroup analyses will be considered exploratory and indicative of differential effects if the interaction term (sub-group * randomised group) has a $P < 0.05$.

- Age
- Sex
- Admission NIHSS score (median split)
- Time from stroke onset (0-6 hours, wake-up stroke, and 6-24 hours)
- Use of thrombolytic agent
- Target vessel occlusion (internal carotid artery, M1 or M2 middle cerebral artery)
- Hypertension (treated hypertension compared to no diagnosis)
- Baseline BP (median split)
- GA maintenance drug (propofol, sevoflurane)
- Reperfusion status (TICI score 0,1,2a v 2b,2c or 3)
- ASPECTS (0-5, 6-8, 9-10)
- Country of recruitment
- Ethnicity

A PP analysis will be performed on the primary, secondary and safety outcomes as the ITT analysis.

6.5 Harms

The most important analysis for harm will be the reporting of sICH, 3-month all-cause mortality and the composite outcome of procedural outcomes. Adverse events (grade 3 and 4) and SAEs will be reported by randomised group.

6.6 Procedure for amendments to the statistical plan

It is intended that all statistical analyses specified in this protocol will be performed. However, it is conceivable that some scheduled analyses may not be performed. In addition, study observations or analysis results may suggest the need for additional statistical analyses of the collected study data. Any revisions to this document prior to database lock will be made in the form of an amendment to the Statistical Analysis Plan. Any deviations or additional analyses that are performed will be summarised in the form of an addendum to the Statistical Analysis Plan. In either case, deviations (subtractions or additions) from the planned statistical analysis will be fully described in the final clinical study report.

6.7 Planned substudies

MASTERSTROKE long-term follow up substudy
MASTERSTROKE haemodynamic substudy
MASTERSTROKE cerebral blood flow interaction substudy

7. References

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2. Campbell D, Deng C, McBryde F, Billing R, Diprose WK, Short TG, Frampton C, Brew S, Barber PA. Protocol for the MAnagement of Systolic blood pressure during Thrombectomy by Endovascular Route for acute ischemic STROKE randomized clinical trial: The MASTERSTROKE trial. International Journal of Stroke 2022; 17(7):810-814

3. Selman CJ, Lee KL, Ferguson KN, Whitehead CL, Manley BJ, Mahar RK. Statistical analyses of ordinal outcomes in randomised controlled trials: a scoping review. Trials 2024; 25: 241

4. Optimising the Analysis of Stroke Trials (OAST) Collaboration; Gray LJ, Bath PM, Collier T. Should stroke trials adjust functional outcome for baseline prognostic factors? Stroke 2009; 40(3): 888-94