CLINICAL TRIAL PROTOCOL

MAnagement of Systolic blood pressure during Thrombectomy by Endovascular Route for acute ischaemic STROKE:

the MASTERSTROKE trial

A multi-centre, patient and assessor-blinded, parallel group, randomised controlled trial (RCT) comparing a 'standard' and 'augmented' systolic blood pressure strategy during general anaesthesia for endovascular thrombectomy in acute ischaemic stroke

Protocol version:	1.4 Dated 8th August 2024
Funding:	ADHB Research Trust, Neurological Foundation of New Zealand, Auckland Medical Research Foundation, Australia New Zealand College of Anaesthetists
Trial registration:	ACTRN12619001274167
Coordinating centre:	Perioperative Research Department of Anaesthesia, Perioperative Directorate Health NZ Te Toka Tumai Auckland
Email:	anaesresearch@adhb.govt.nz
Global Sponsor:	Dr Doug Campbell, Health NZ Te Toka Tumai Auckland
Australian Sponsor:	The University of Queensland
Ethical approvals:	NZ Ethics - 8892 Health and Disability Ethics Committee Australian Ethics – HREC/2020/QMS/70532, Metro South Human Research Ethics Committee

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ABBREVIATIONS

ANZCA = Australian and New Zealand College of Anaesthetists
ANZCA CTN = Australian and New Zealand College of Anaesthetists Clinical Trials Network
ASA-PS = American Society of Anaesthesiologists- Physical Status
CBF = Cerebral Blood Flow
$CMRO_2$ = Cerebral Metabolic Rate for Oxygen
CI = Confidence Interval
CS/LA = Conscious Sedation or Local Anaesthesia
CT = Computerised Tomography
DAH_{90} = Days Alive at Home at 90 days
DMC = Data Monitoring Committee
DWI = Diffusion Weighted Imaging
EVT = EndoVascular Thrombectomy
GA = General Anaesthesia
HDU = High Dependency Unit
ICA = Internal Carotid Artery
ICU = Intensive Care Unit
INR = Interventional NeuroRadiologist
IQR = Interquartile range
LVO = Large Vessel Occlusion
MAP = Mean Arterial Pressure
MCA = Middle Cerebral Artery
MASTERSTROKE = MAnagement of Systolic blood pressure during Thrombectomy by Endovascular Route for acute ischaemic STROKE
mRS = modified Rankin Score
NIHSS = National Institute of Health Stroke Score
OR = Odds Ratio
PACU = Post Anaesthesia Recovery Unit
PI = Principal investigator
RCT = Randomised Control Trial
RR = Relative Risk
SC = Steering Committee
SBP = Systolic Blood Pressure
sICH = symptomatic IntraCranial Haemorrhage

1. ADMINISTRATIVE INFORMATION

1.1 Title

A multi-centre, patient and assessor-blinded, parallel group, randomised controlled trial (RCT) comparing a 'standard' and 'augmented' systolic blood pressure strategy during general anaesthesia for endovascular thrombectomy (EVT) in acute ischaemic stroke.

1.2 Trial registration

ANZCTRN: ACTRN12619001274167
All trial information is available online on the Australian and New Zealand Clinical Trials Registry: http://www.anzctr.org.au/

1.3 Protocol version

Version 1.4

1.4 Funding

This study is funded by Auckland District Health Board Research Trust, The Neurological Foundation of New Zealand, Auckland Medical Research Foundation and Australia New Zealand College of Anaesthetists.

1.5 Roles and responsibilities

1.5.1 Principal Investigator

Name: Dr Doug Campbell
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1.5.2 Steering Committee

Alan Barber (AB)
Stefan Brew (SB)
Doug Campbell (DC)
Carolyn Deng (CD)
Tim Short (TS)
Davina McAllister (DM)
David Highton (DH)

1.5.3 Protocol

The protocol was written by DC, CD, AB according to the SPIRIT 2013 guidelines.

1.5.4 Operations Committee

Doug Campbell

Davina McAllister

Incumbent - NeuroAnaesthesia Fellow

Incumbent – Neurology Research Fellow

1.5.5 Data Safety Monitoring Committee

Dr Barry Snow (Chair), Neurologist, Auckland City Hospital
Prof Jamie Sleigh, Anaesthetist, Waikato Hospital
Dr Yannan Jiang, Senior Research fellow, Department of Statistics,

1.5.6 Endpoint Adjudication Committee

Dr Shane Lee, Interventional Neuroradiology, Auckland City Hospital
Dr Tin Chiu, Anaesthetist, Auckland City Hospital
Mr Jason Correia, Neurosurgeon, Auckland City Hospital

1.5.7 Trial statistician

Professor Chris Frampton

1.5.8 Role of the funders

This is an investigator-initiated study. The SC will take responsibility for study design and oversight. The funders will have no role in study design, data collection, management, analysis, data interpretation, manuscript writing, or in the decision to submit manuscripts for publication.

1.5.9 Trial Sponsor

New Zealand Sponsor: Dr Doug Campbell will act as trial sponsor
Australian Sponsor: University of Queensland

1.5.10 Study Coordinator, Coordinating/Data Management centre

Trial Manager: Ms. Davina McAllister
Coordinating/
Perioperative Research
Department of Anaesthesia, Perioperative Directorate
Te Whatu Ora Te Toka Tumai Auckland

2 INTRODUCTION

2.1 Background and rationale

Key concepts

- EVT for LVO acute ischaemic stroke is a highly effective therapy for reducing disability at 3 months
- There is direct evidence that relative hypotension worsens outcomes during ECR
- It is unknown if increased SBP during GA improves outcomes.
- A large RCT is the most robust way to assess the treatment effect.

Significance of the health issue

Stroke is the third most common cause of death in New Zealand and is one of the leading causes of long-term disability at all ages [11]. The lifetime costs of a stroke per person were estimated at $73,600 in 2009, with a total cost of $450 million per year in New Zealand [12]. Large vessel anterior circulation stroke is a devastating disease with lifelong disability, dependence on others for care and very high mortality. The burden on patients, carers, health care providers and society will be higher in these most severe strokes.

The recent introduction of EVT has resulted in a large improvement in outcomes in these patients. New Zealand is at the forefront of introducing this new therapy to patients with annual 28 PSI procedures per million population performed in 2017. During a similar timeframe, the UK performed 7 per million population annually [13]. Essential principles for high quality care are a) rapid delivery of patients to tertiary centres providing PSI for diagnosis and b) definitive treatment by recanalisation of target vessel. The number of PSI procedures is increasing exponentially with faster presentation to hospital, more rapid imaging and diagnosis and extended therapeutic windows [14]. This means any further improvement in care will be increasingly available for New Zealanders. Māori patients are younger, have a higher incidence of stroke and worse outcomes [16-18]. In the Northern Region of New Zealand, Māori represented 17.5% of all ECR patients and were younger than non-Māori patients [12]. Any further improvements in ECR care will confer extra improvements in outcome in Māori over non-Māori in anterior circulation stroke.

Potential to advance knowledge

Systems of care to deliver eligible patients have reduced time from stroke onset to recanalisation since 2011. Rates for successful recanalisation (TICI 2b/3, over 50% vessel patency) are up to 88% in some New Zealand centres [19]. The DAWN [2] and DEFUSE-3 [3] trials have extended the therapeutic window from 6 hours to 24 hours in selected patients. Improvements in Intervention technology, further extensions of the therapeutic window or advances in thrombolytic therapy have limited ability to further improve current outcomes. A plausible strategy to improve outcomes in all eligible patients is to initiate therapies that protect the ischaemic penumbra until target vessel recanalisation is possible. A recent review article outlined investigational therapies that increase perfusion or oxygen delivery, or alternatively reduce tissue energy requirements in the ischaemic penumbra[15].

Table 1 | **Potential nonpharmacological interventions to freeze the ischaemic penumbra**

Intervention	Mechanism of penumbral protection	Effect on infarct volume in rodents	Penumbral freezing directly documented	Translatability	Ongoing RCTs directly testing the penumbral freezing paradigm
Normobaric oxygen (NBO)	Increased oxygen delivery	Strong effects if given early after tMCAO; little or no effect in pMCAO or tMCAO > 3 h	Yes (also in humans)	Excellent (including pre-hospital)	One (PROOF)[a]
Perfluorocarbons (PFCs)	Increased oxygen delivery	Strong effect in combination with NBO (mainly in tMCAO), but few good-quality studies	Yes	Excellent (including pre-hospital)	None
Transient descending aortic balloon occlusion (TAO)	Increased collateral perfusion	Strong effects in both tMCAO and pMCAO, but few studies published	No	Limited (complex logistics)	One (RESCUE)[a]
Remote ischaemic perconditioning (RIPerC)	Increased collateral perfusion	Strong effects (stronger with tMCAO than with pMCAO), but few studies published	No	Excellent (including pre-hospital)	None
Sensory stimulation	Increased collateral perfusion	Strong effects in rats (both tMCAO and pMCAO) if given early	No	Unclear, as sensory stimulation is detrimental in mice or if started late, but could be started pre-hospital	None
Sphenopalatine ganglion stimulation (SPGS)	Increased collateral perfusion	Clear effects (only pMCAO tested)	Yes	Good, but difficult to apply in the field	None
Therapeutic hypothermia	Reduced tissue energy requirements	Strong effects; larger in tMCAO (any duration) than in pMCAO and larger with deep hypothermia	No	Good, but deep hypothermia is associated with more adverse effects; pre-hospital delivery difficult	One (ICTuS-3)[a]
Cathodal transcranial direct cortical stimulation (C-tDCS)	Inhibition of peri-infarct depolarizations	Mild to moderate effects in both tMCAO and pMCAO, but few studies published	No	Excellent (including pre-hospital)[b]	One (STICA)[a]

pMCAO, permanent middle cerebral artery occlusion; RCT, randomized controlled trial; tMCAO, temporary MCAO. [a]See main text for details. [b]Given its dual effects — that is, both freezing the penumbra and preventing reperfusion injury — hypothermia can and probably should be administered both before and after recanalization (see main text for details).

Table 1. Investigational therapies that increase penumbral oxygen delivery, penumbral blood flow, or reduce tissue oxygen demand. Reproduced from ref 15.

In New Zealand, an anaesthetist is present at all PSI case, and 90% of procedures are performed under general anaesthesia. This presents an ideal opportunity to investigate pharmacological or physiological interventions used frequently during anaesthesia to increase supply (vasopressors, IV fluid, cerebral vasodilators [sevoflurane, desflurane]) or reduce demand (propofol, sevoflurane, desflurane, hypothermia) during the hyperacute ischaemic period.

Demonstration of the research gap

Internationally, the debate regarding the use of pharmacological or physiological interventions during PSI has centred on observational data suggesting GA confers worse outcomes than local anaesthesia or conscious sedation. This outcome difference could be accounted for by selection bias, treatment delay, confounding by relative hypotension or direct drug effects. A recent individual meta-analysis of observational data within PSI trials was able to adjust for baseline severity differences and treatment delay. The worse functional outcomes at 3 months after GA compared to CS/LA remained with a covariate adjusted OR of 1.53 (CI 1.14-2.04, p=0.0044). None of these trials reported anaesthesia drugs used or associated physiology (including SBP) making further inference difficult. A meta-analysis by Campbell and Barber of four RCTs [5-8] of GA vs CS/LA, where blood pressure (BP) management was equivalent between groups showed functional outcomes at 3 months were superior in the GA group with an OR of 0.58 (CI 0.39-0.88).

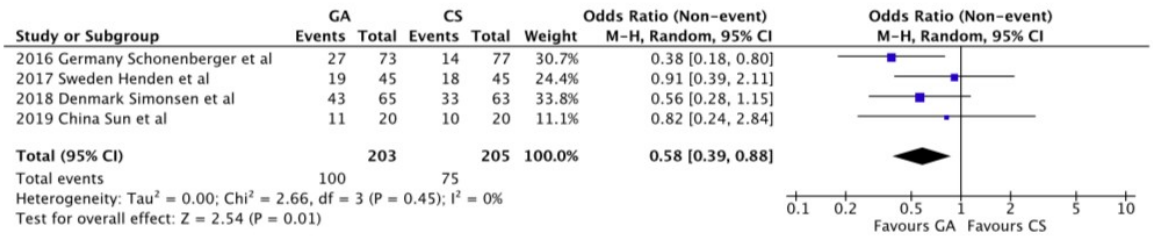

Figure 1. Meta-analysis of four RCTs of CS v GA looking at good functional outcome at 3 months in acute ischemic stroke

An explanation of the differences in outcome in the observational data is that relative hypotension confounded the studies and that relative hypotension is harmful rather than GA *per se*. Normalising BP would eliminate the harm, but what effect would augmenting BP in this setting have? In the meta-analysis by Campbell et al, GA was superior to CS/LA but BP was equivalent in these studies. An important difference is that some anaesthesia agents (sevoflurane, desflurane) have a profound effect impairing normal cerebral autoregulation (and propofol to a lesser degree) and are cerebral vasodilators. The superiority of GA in this setting could be due to equivalent BP in the presence of cerebral vasodilation and impaired autoregulation providing flow augmentation. Again, what effect would augmenting BP in this setting have?

Usual SBP management in a national dataset has a mean SBP of 141 mm Hg. In published randomised comparisons between GA and CS where GA outcomes were not inferior, mean SBP in these cohorts ranged from 139 to 146 mm Hg. Current stroke guidelines recommend an upper limit of 185mmHg after thrombolysis to reduce haemorrhagic complications. Therefore, we have chosen 140 mm Hg +- 10 mm Hg and 170 mm Hg +- 10 mm Hg as the comparators. These conform to SBP targets within the range of usual national and international practice.

2.2 Aims

The aim of this study is to establish the optimal approach to SBP management for adults undergoing general anaesthesia during endovascular clot retrieval for acute ischaemic stroke by comparing the effect of two SBP strategies on functional recovery at 90 days.

We hypothesise that in adults who fulfill the eligibility criteria below that an 'augmented' SBP regime will result in improved disability at 90 days as measured by mRS.

2.3 Trial design

A multi-centre, patient and assessor-blinded, parallel group, randomised controlled trial (RCT) comparing a 'standard' and 'augmented' systolic blood pressure strategy during general anaesthesia for endovascular clot retrieval in acute ischaemic stroke.
A pre-defined sub-group analysis will compare maintenance of anaesthesia with intravenous propofol v inhalational sevoflurane.

3 METHODS: PARTICIPANTS, INTERVENTIONS AND OUTCOMES

3.1 Study setting

This study will be conducted in angiography suites in New Zealand, Australia and the Netherlands.

3.2 Eligibility criteria

Adults (≥18 yrs.) who fulfill all of the following inclusion criteria, none of the exclusion criteria, and have undergone an appropriate consenting process.

3.2.1 Inclusion criteria

Patients diagnosed with anterior circulation stroke (ICA or proximal M1 or M2 segment of MCA) treated with ECR within 6 hrs. of stroke onset **and** ECR patients presenting within 6-24 hours with 'wake up' stroke ; or CT with favourable penumbra on CT perfusion scanning.

3.2.2 Exclusion criteria

- pre-stroke mRS>=3
- not having GA
- 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; e.g. Acute Ischaemic Stroke associated with major medical procedures such as coronary artery stenting and coronary artery bypass.

3.3 Interventions

3.3.1 Study interventions

The procedural anaesthetist will be asked to disclose maintenance anaesthesia agent prior to randomisation. Following randomisation, participants will be allocated to one of two haemodynamic strategies from ECR until recanalisation.

'Standard' – SBP at 140+-10 mm Hg
'Augmented' - SBP at 170+-10 mm Hg

Techniques used to target SBP will be at the discretion of the procedural anaesthetist but will include vasopressors, intravenous fluids, titration of anaesthetic maintenance drugs and use of other vasoactive drugs. General anaesthesia will be based on an intubated patient with control of haemodynamic physiology as described, but also ventilation to normocarbia ($ETCO_2$ 4.5-6.0 kPa or $PaCO_2$ 4.5-6.0 kPa) and maintenance of normothermia and normoglycaemia. Doses and timing of administration will be recorded on the electronic anaesthesia record and data transcribed to the CRF.

3.3.2 Criteria for discontinuing or modifying allocated interventions

The duration of the study intervention will be until the target vessel is recanalised or no further attempts at recanalisation are possible. If there is an unexpected anaesthesia or

medical event, or procedural complication e.g. vessel dissection or ICH, requiring change of SBP for safety reasons, then the study intervention can be terminated and a new clinical SBP can be targeted.

3.3.3 Strategies to improve adherence to protocols

The site PIs will take primary responsibility for training local staff and will use study tools provided by the coordinating centre. Early on-site data monitoring will be performed by the MasterStroke Project manager, from the coordinating centre, to ensure protocol compliance is achieved. De-Identified Anaesthesia record data, which are sent to the project office, with study identifier will be audited by an unblinded auditor (with no access to study outcome data) for regular trial adherence and separation reporting.

3.3.4 Concomitant therapies

There are no restrictions to concomitant treatments provided to patients in this study.

3.4 Outcomes

3.4.1 Primary outcome

The primary outcome is improvement in disability measured by ordinal shift in the modified Rankin Score assessed at day 90 and assessed by ordinal shift analysis.

3.4.2 Secondary outcomes

1. Excellent functional outcome as measured by a modified Rankin of 0, or 1 at 90 days
2. Independent functional outcome as measured by a modified Rankin of 0, 1 or 2 at 90 days
3. The number of days a participant spends at home in the first 90 days post-stroke (home days/DAH_{90})
4. All-cause mortality at 90 days
5. Intra-procedural complications (target vessel dissection, intracerebral haemorrhage, groin haematoma)
6. Symptomatic intracranial haemorrhage within 36 hours of treatment.

3.4.3 Physiological outcomes

1. Proportion of time within group allocation range
2. Mean procedural SBP
3. Mean procedural DBP
4. Mean procedural MAP
5. Cumulative time SBP < 140 mm Hg
6. Mean procedural HR
7. Mean procedural SpO_2
8. Mean procedural $ETCO_2$
9. Blood glucose
10. Temperature

3.4.4 Process of care measures

1. Groin puncture to recanalisation time
2. Airway type
3. Total time spent in the PACU
4. Total time spent in HDU/ICU
5. HLOS

3.5 Sample size

Statistical modeling of ordinal shift of mRS based on data on good functional recovery data (mRS 0-2) showed that recruiting 550 participants will provide 90% power to detect the proportion of patients who will improve 0.5 points on the modified Rankin Scale at 3 months including 10% loss to follow up. This is equivalent to a group 1 proportion, $P_1 = 0.58$ (current national data) improving to $P_2 = 0.68$, a clinically important improvement of 10% in good functional recovery (mRS 0-2) at 3 months.

3.6 Recruitment

All hospitals participating in this study have significant experience undertaking large scale, investigator-initiated studies. Many MASTERSTROKE sites are previous BALANCED Trial sites which required anaesthetists to simultaneously target a depth of anaesthesia and haemodynamic target. The new Australian sites have significant experience running other large RCTs through the Australian and New Zealand College of Anaesthesia's Clinical Trials Network.

On the basis of a conservative estimate of 6 participating sites recruiting an average of 3 eligible patients per month, recruitment of 550 participants will be completed in less than 31 months. The number of sites required and the expected recruitment rate will be refined based on the observed recruitment rate in the initial trial recruitment phase. All sites will receive regular study newsletters and support to ensure adequate recruitment is achieved All sites will receive individual site group allocation adherence reports. Based on our previous experience conducting similar large-scale clinical trials of this nature, our recruitment timelines are appropriately conservative.

4 METHODS: ASSIGNMENT OF INTERVENTIONS

4.1 Sequence generation

A permuted block randomisation method with block size of 8, will be used to allocate eligible patients in a 1:1 ratio to 'standard' or 'augmented' haemodynamic strategies. This has been aligned into the ALEA trial data base.

4.2 Allocation concealment

ALEA clinical trials database has been set up to provide electronic sequential randomisation as per 4.1 and concealed from participants, investigators and outcome assessors.

4.3 Implementation

Following determination of screening eligibility, and consent, subjects will be randomized, on a one-to-one basis,to either to 'standard' or 'augmented' haemodynamic strategies. The Participants will be enrolled by clinical staff at the study sites.

4.4 Blinding

Blinding of treatment providers is not possible.

Participants, interventional neuroradiologists, neurologists and all outcome assessors will be blinded.

One unblinded research coordinator at each site will collect SBP related to the intraprocedural data points.

All other site researchers, investigators and research coordinators, will be remain blinded as to treatment allocation and will collect data relating to primary and secondary outcomes. They will remain blind to group allocation by avoiding review of the intraoperative section of the medical record.

Unblinding of patients or observers during the trial is not envisaged as the attending anaesthetist will be aware of group assignment and the assigned treatment will be recorded in the medical record. If unblinding is deemed necessary, research staff at the participating site will contact the Trial Coordinating Centre for approval.

5 METHODS: DATA COLLECTION, MANAGEMENT AND ANALYSIS

5.1 Data collection methods

Baseline data will include patient demographics (age, sex, ethnicity), ASA status, chronic comorbidities, medications, thrombolysis administration, baseline NIHSS, anatomical stroke territory, partial or complete occlusion, ,. Baseline physiological parameters will include SpO_2, respiratory rate, temperature, heart rate and blood pressure. Data will be collected by trained research coordinators at each site. DAH_{30} will be calculated from the electronic health record, and information provided by the patient and/or their next of kin as soon as possible after 30 days have elapsed following the day of surgery. Additionally, for New Zealand participants, outcome data will be obtained from the Ministry of Health (MoH) National Minimum Dataset (NMDS) linked with baseline and exposure data from the MoH NMDS and the anaesthesia record. Data quality and protocol standardisation will be optimised by arranging a start-up meeting, providing an early on-site monitoring visit, regular feedback to each centre via phone and the trial web-site, and a regular newsletter. A complete study procedures manual will be produced. All study personnel will have 24-hour access to the study coordinating centre to resolve any questions.

5.2 Data management

A central electronic database will be designed, constructed and maintained for the purposes of the trial. The structure and data flow of the database will follow that of the case report form. Data entry onto the database at each participating site will be via a secure, password protected, online web-based portal. The database will have the facility for transmitting data queries and requests for missing data, directly or via email notifications, to site research coordinators, as well as data interrogation and cross-checking algorithms to minimize incorrect data entries and maximize data capture and completeness. Data at each site will be entered into the portal either via an electronic case report form networked to the portal or after data entry onto a paper case report form.

Access to study data at all sites will be restricted to approved trial personnel. Electronic data will be password protected while paper records will be kept in locked cabinets/offices, in compliance with ICH-GCP guidelines and local policies of participating sites. Study data must be kept at the site for at least 15 years following the date of completion of the trial.

The study website will incorporate internal consistency checks, and require manual verification of extreme data values. Study data will be stored for 10 years in New Zealand

and 15 years in Australia in a secure archive as per usual practice at each recruiting site. Australian data will be held at the University of Queensland via UQ RDM as per the UQ Research Data Management Policy.

5.3 Statistical methods

5.3.1 Methods for analysing the primary outcomes and secondary outcomes

Analyses will be performed in the intention-to- treat population. A full statistical analysis plan (SAP) will be lodged on ANZCTR and the trial website before recruitment is complete and before unblinding of the database.

5.3.2 Methods for additional analyses

Baseline covariates will include age, gender, ethnicity, country of recruitment, baseline NIHSS, stroke territory, partial or complete vessel obstruction, use of alteplase, maintenance GA agent used.

5.3.3 Analysis population

All analyses will be conducted on an intention-to treat basis with no imputation of missing data. A secondary per protocol analysis is planned.

6 METHODS: MONITORING

6.1 Data monitoring

6.1.1 Composition and governance

An independent Data Safety Monitoring Committee (DSMC), consisting of experts in anaesthesia, neurology, clinical research and biostatistics will be established before patient enrolment and will review all trial protocols. A set of DSMC guidelines and a DSMC Charter will be prepared by the SC and signed by the members of the DSMC before the trial commences.

6.1.2 Interim analyses

We will perform an interim analysis for safety after 300 participants have been recruited. Primary safety outcome will be mRS at 90 days and secondary safety outcomes 90-day all-cause mortality, procedural complications and sICH. All outcome variables will be reviewed by the DMC.

6.2 Harms

Patients undergoing ECR may experience complications as a direct result of the procedure. **All** study outcomes, serious adverse events (SAE); for example pneumonia leading to death, and any adverse events (AE) which are considered to be potentially causally related to the study intervention or are otherwise of concern in the investigator's judgment will be reported.

ADVERSE EVENTS

Reporting adverse events to national regulatory authorities and IRBs / Ethics Committees (EC) will be performed in accordance with the applicable regulations and the local requirements.

The Investigator will submit all STUDY OUTCOMES noted above and SAE reports to the Sponsor in a timely manner.

Serious Adverse Events (SAE):

Adverse event that led to any of the following:

a) death,

b) serious deterioration in the health of the subject, users, or other persons ad defined by one or more of the following:

1) a life-threatening illness or injury, or

2) a permanent impairment of a body structure or a body function including chronic diseases, or

3) in-patient or prolonged hospitalization, or

4) medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function,

c) foetal distress, foetal death or a congenital abnormality or birth defect including physical or mental impairment

NOTE Planned hospitalization for a pre-existing condition, or a procedure required by the CIP, without serious deterioration in health, is not considered a serious adverse event.

All adverse events will be recorded on the CRF by the Investigator or his/her designee. However, it is the responsibility of the Investigator to ensure that all information is correct and appropriately documented.

All adverse events should be followed until they are adequately resolved or explained. In the unusual circumstance that an AE has not resolved by the time of the subject's completion of the study, an explanation will be entered on the appropriate CRF.

Adverse Event Severity

The Investigator will use the following definitions to rate the severity of each adverse event:

Table 6. Adverse Event Severity Severity	**Description**
Mild	• Awareness of a sign or symptom that does not interfere with the patient's usual activity or is transient, resolved without treatment and • No sequelae
Moderate	• Interferes with the patient's usual activity and/or • Requires symptomatic treatment
Severe	• Symptom(s) causing severe discomfort and • Significant impact of the patient's usual activity and Requires treatment

Intervention-Related

The relationship of the adverse event to the investigational intervention will be assessed according to the following definitions:

Adverse Event Intervention Relationship	**Description**
Definite	The adverse event is clearly related to the investigational Intervention: the event has a temporal relationship to the investigational Intervention, follows a known pattern of response, or is otherwise logically related to the investigational Intervention, and no alternative cause is present.
Probable	The adverse event is likely related to the investigational Intervention: the event has a temporal relationship to the investigational Intervention, follows a known or suspected pattern of response, or is otherwise logically related to the investigational Intervention, but an alternative cause may be present.
Not Likely	The adverse event is unlikely related to the investigational Intervention: the event does not follow a clear temporal relationship to the investigational Intervention or does not follow a known pattern of response or is otherwise likely to be due to the subject's clinical state or other modes of therapy.
Not Related	The adverse event is clearly not related to the investigational Intervention: the event has no temporal or other relationship to the administration of the investigational Intervention, follows no known or suspected pattern of response, and an alternative cause is present.
Unknown	Unable to determine the relationship based on all available information.

Procedure-Related

The relationship of the adverse event to the procedure will be assessed according to the following definitions:

Adverse Event Procedure Relationship

Relationship	Description
Definite	The adverse event is clearly related to the procedure: the event has a temporal relationship to the procedure, follows a known pattern of response, or is otherwise logically related to the procedure, and no alternative cause is present.
Probable	The adverse event is likely related to the procedure: the event has a temporal relationship to the procedure, follows a known or suspected pattern of response, or is otherwise logically related to the procedure, but an alternative cause may be present.
Not Likely	The adverse event is unlikely related to the procedure: the event does not follow a clear temporal relationship to the procedure or does not follow a known pattern of response or is otherwise likely to be due to the subject's clinical state or other modes of therapy.
Not Related	The adverse event is clearly not related to the procedure: the event has no temporal or other relationship to the procedure, follows no known or suspected pattern of response, and an alternative cause is present.
Unknown	Unable to determine the relationship based on all available information.

6.3 Monitoring of clinical trial sites and investigators

The MasterStroke Trial Manager /monitors and/or designees will perform clinical trial monitoring of 100% of randomized subjects. This monitoring will include review of eCRF data with verification to the source documentation.

Information on the eCRF must match the same information on the source documents or a data query will be issued. Queries will be resolved with the site.

If the MASTERSTROKE Trial Manager determines that an Investigator is not in compliance with any requirements outlined in this investigational plan or the investigator agreement, the MASTERSTROKE Trial Manager, in conjunction with the local Sponsor shall promptly secure compliance.

In addition, assessments including overall compliance with the investigational plan, accurate eCRFs, and compliance with Good Clinical Practices (GCP), ECs and local regulatory requirements will be monitored on an ongoing basis by the MASTERSTROKE Trial Manager and/or its designees.

Periodic monitoring visits will be made at the investigational site throughout the clinical trial to ensure that the Investigator obligations are fulfilled and all applicable regulations and guidelines are being followed. These visits will ensure that the facilities are still acceptable, the protocol is being followed, the IRB / EC and local authorities have been notified of approved protocol changes as required, complete records are being maintained, appropriate and timely reports have been made to the MASTERSTROKE Trial Manager and/or its designees and the IRB / EC.

The Sponsor will reserve the right to remove either the Investigator or the investigational site from the trial for noncompliance with the protocol or regulations.

7 ETHICS AND DISSEMINATION

7.1 Research ethics approval

Research ethics approval will be obtained prior to the start of the study at each institution from the responsible local and/or national human research ethics committee.

7.2 Protocol amendments

Protocol amendments will be updated on relevant clinical trial registries by the Study Coordinator. Amendments will be communicated by regular newsletters, teleconferences, and emails to site Principal Investigators and Research Coordinators.

7.3 Consent

7.3.1 New Zealand consent model

Patients presenting for ECR may be incompetent to consent because of the presenting illness. In addition, the urgent requirement for medical treatment leads to a time pressured scenario where full explanation, understanding and reflection of the risks and benefits of participating can be assimilated. In New Zealand, we will use two physician best interest agreement. The two arms of the trial are within the range of normal clinical practice so inclusion in the trial adds no further burden to the patient. National Health and Disability Ethics Committee approval for the consent process was sought prior to study commencement.

7.3.2 Australian consent model

As in the New Zealand patient cohort, patients presenting for ECR may be incompetent to consent because of the presenting illness. Unlike New Zealand, Australia does not facilitate a two-physician best interest agreement. In Australia, the proposed consent model will be based on the guidelines set out in the National Statement section 4.4; which is to gain consent from the individual where possible and substitute decision-makers where it is not; and provide an opportunity to withdraw if the participant's capacity changes.

A Participant Information Sheet and Consent form along with a Substitute Decision Maker Verbal and In Person Consent Forms will be utilised to obtain consent before enrolment into the research. Written consent to continue will then be obtained later directly from the patient, if not possible prior, when and if the patient regains capacity. If the patient chooses not to continue in the trial, all data collected prior to this point will be withdrawn and will not be used in analysis.

In cases where no Substitute Decision Maker is available, a limited waiver of consent will be sought from the HREC to enroll patients, providing a Consent to Continue is obtained later from the patient, when and if the patient regains capacity.

7.4 Confidentiality

Patients will be allocated a unique study number. The site research coordinator will keep an enrolment log that includes the patients' details and a unique study number. Study data will be obtained from the patients' medical records. Study data and enrolment logs will be kept separately. Contact details for participants and their next of kin will be provided to the Research Office and home days and mRS categorisation will be obtained by a blinded central assessor at the Research Office by questioning at routine clinic visits or phoning participants and / or their next of kin if a clinic visit is not scheduled at 90 days post-stroke.

At all times throughout this study, all parties shall strictly observe the confidentiality of subject's health information. All data shall be secured against unauthorized access. Each subject participating in this study will be assigned a unique identifier. All eCRFs will be tracked, evaluated, and stored using only this unique identifier.

The Investigator will maintain a confidential study subject list identifying all enrolled subjects. This list will contain the assigned study subject's unique identifier and name. The Investigator bears responsibility for keeping this list confidential. This list will not be provided to the study Sponsor and is only to be used at the study center.

Monitors and auditors will have access to the study subject list and other personally identifying information of study subjects to ensure that data reported in the eCRFs corresponds to the person documented on the consent form and the information contained in the original source documents. Such personal identifying information may include, but is not limited to, the subject's name, address, date of birth, gender, race and medical record number.

Any source documents copied for monitoring purposes by the MASTERSTROKE Trial Manager or designee, will be identified by using the assigned subject's unique identifier and obscuring personal identifying data in an effort to protect subject confidentiality.

7.5 Declaration of interests

All study investigators have confirmed that they do not have any financial or other conflicts of interest to declare in relation to this study.

7.6 Access to data

The Steering Committee will oversee data sharing with the following groups: Steering Committee members, site investigators, sub-study and sub-analysis groups formed by the Steering Committee, and external investigators. Details will be found in a trial data sharing statement.

The final trial dataset will be available to the Steering Committee. Other co-investigators will have access to site level data and jurisdictional data. There are no contractual agreements in place which limit access to study data.

To allow for the use of the information derived from this study and to ensure compliance with applicable regulations, the Investigator is obliged to provide MASTERSTROKE Trial Steering Committee with all data developed from this study.

MASTERSTROKE Trial Steering Committee will have final approval authority on the proposed content for an abstract or manuscript submitted for presentation / publication.

Investigators will submit abstracts, articles, and scientific presentations to the MASTERSTROKE Trial Steering at least sixty (60) days in advance for comment regarding consistency with monitored database and to protect the Sponsor's Intellectual Property.

7.7 Post-intervention care

After completion of the intervention patients will receive standard treatment. Haemodynamic goals post recanalisation will be determined as per local institutional practice and therapies to treat hypertension or hypotension within 24 hours will be recorded in the CRF. Participants will be transferred to PACU, HDU or ICU at the discretion of the procedural anaesthetist, INR and neurologist, and to the Stroke Unit thereafter.

7.8 Dissemination policy

The trial will be conducted in the name of the MASTERSTROKE Investigators and the ANZCA CTN. The principal publications from the trial will be in the name of the MASTERSTROKE Investigators with full credit assigned to all collaborating investigators, research coordinators and institutions. Where individuals' names are required for publication, they will be the members of the management committee, with the PI listed first and subsequent authors listed alphabetically. Members of additional committees with a major contribution e.g. DSMB will be listed by PubMed attribution. Funding bodies will be acknowledged in the publication.

7.9 Authorship eligibility

Authorship of the primary manuscript and trial methodology paper will be attributed to the principal investigator, investigators, trial statistician, and trial manager. First author will be Doug Campbell, last author Prof Alan Barber. Second author to be discussed at Steering Committee.

Where permitted by journal policy, authorship will also be attributed to "The MASTERSTROKE Study investigators and the Australian and New Zealand College of Anaesthetists Clinical Trials Network". Authorship may be extended or altered (e.g., to include site investigators who make substantial contributions to the trial), according to a majority vote of the Steering Committee. The order of the authors on the primary manuscript and trial methodology paper will be determined by the Writing Committee.

Members of the trial committees (i.e., Steering Committee, Operations Committee, Data Quality Committee, Data and Safety Monitoring Committee, Endpoint Adjudication Committee and Writing Committee) will be listed in an appendix to the primary manuscript. The chair will be listed first with other members in alphabetical order. Site investigators and coordinators of sites randomising at least one participant will be listed in an appendix to the primary manuscript. The number of site investigators and coordinators that may be listed for each site will be decided by the Writing Committee based on final site recruitment to the trial, and site investigators will be advised. Regions and sites will be listed alphabetically. Site investigators and coordinators will be listed in the order determined by the site.

Authorship of sub-studies and sub-analyses will be determined by the Steering Committee. Authorship may be offered to investigators and statisticians who led sub-studies and sub-analyses, and may be offered to Steering Committee members and site principal investigators who made substantial contributions to the trial.

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