An investigator initiated and conducted, prospective, multicentre, randomised, outcome-blinded study of blood pressure lowering in patients with acute ischaemic stroke with successful recanalisation after endovascular mechanical thrombectomy

Enchanted2

Enhanced Control of Hypertension and Thrombectomy Stroke Study

Enchanted-MT

Statistical Analysis Plan

Version: 1.0 (Final)

Date: 21 June 2022

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Trial registration: ClinicalTrials.gov (NCT04140110)

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Contents

1 Administrative information

1.1 Study identifiers

- Protocol Version: 3.0, Date: 18 Aug 2020
- Chinese Trial Registry: ChiCTR1900027785
- ClinicalTrials.gov register Identifier: NCT04140110

1.2 Revision history

Version	Date	Details
0.1 (draft)	2 Jun 2022	First draft by Laurent adapted from ENCHANTED SAP
0.2 (draft)	16 Jun 2022	New version following review by Lili and Craig
1.0 (final)	21 Jun 2022	Final version

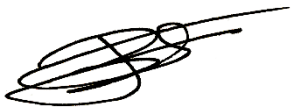
1.3 Contributors to the statistical analysis plan

1.3.1 Roles and responsibilities

Name and ORCID	Affiliation	Role on study	SAP contribution
Prof Laurent Billot	The George Institute for Global Health, UNSW Sydney	Study statistician	Prepared initial draft and revisions
Dr Lili Song	The George Institute China; The George Institute for Global Health, Faculty of Medicine, UNSW Sydney	Co-investigator Project Lead	Reviewed all versions
Dr Pengfei Yang	Changhai Hospital, Navy Medical University, Shanghai, China	Co-investigator Co-Project Lead	Reviewed all versions
Prof Jianmin Liu	Changhai Hospital, Navy Medical University, Shanghai, China	Co-Principal Investigator	Reviewed all versions
Prof Craig Anderson	The George Institute for Global Health, Faculty of Medicine, UNSW Sydney	Co-Principal Investigator	Reviewed all versions

1.3.2 Approvals

The undersigned have reviewed this plan, approve it as final and as consistent with the requirements of the protocol as it applies to their respective areas. They also find it to be compliant with International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) topic E9 Statistical Principles for Clinical Trials, and confirm that this analysis plan was developed in a completely blinded manner, that is without knowledge of the effect of the intervention(s) being assessed.

Name	Signature	Date
Prof Laurent Billot		21 June 2022
Dr Lili Song		21 June 2022
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2 Introduction

2.1 Study synopsis

The second, ENhanced Control of Hypertension And Thrombectomy strokE stuDy (ENCHANTED2) is an international, multicentre, prospective, randomised, open-label, blinded-endpoint assessed (PROBE) clinical trial, assessing different approaches to intensities of blood pressure (BP) control in a high-risk patient population with acute stroke. There are two nested substudies evaluating different antithrombotic approaches for secondary prevention. The main objective is to determine the effectiveness of more intensive BP lowering (systolic BP [SBP] target <120 mmHg) as compared to a higher BP management (target SBP 140-180mmHg) on functional outcome in patients who have had successful recanalisation with endovascular (mechanical thrombectomy) therapy (EVT) for acute ischaemic stroke (AIS) due to large vessel occlusion (LVO). The full protocol is currently under peer review with a journal, since submission in May 2022.[1]

2.2 Study population

This study is being conducted at approximately 60 hospital sites in China, with plans to include additional sites in Australia and the UK.

2.2.1 Inclusion Criteria

- Age ≥18 years
- Diagnosis of AIS with LVO confirmed by brain imaging
- To receive EVT <24 hours after the onset of symptoms, according to local guidelines
- Successful recanalisation (defined by expanded treatment in cerebral infarction [eTICI] score of ≥2b) after EVT (See Appendix 1)
- Sustained SBP ≥140 mmHg (defined as 2 successive readings <10 mins apart) within 3 hours after recanalisation
- Provide written informed consent (or from an approved surrogate).

2.2.2 Exclusion Criteria

- Unlikely to potentially benefit from therapy (e.g. advanced dementia) or very high likelihood of death within 24 hours post-EVT, judged by responsible treating clinician
- Other medical illness that might interfere with outcome assessments and follow-up (e.g. known significant pre-stroke disability [modified Rankin scale (mRS) scores 3-5), advanced cancer, and renal failure)
- Definite indication/contraindication to different intensities of BP lowering treatment
- Specific contraindications to any of the BP agents to be used (e.g., patients who are hypersensitive [allergic] to any of the ingredients)

- Patients with aortic isthmus stenosis and arteriovenous shunt (exception: patients with haemodynamically inactive dialysis shunt)
- Women who are lactating
- Currently participating in another trial which would interfere with outcome assessments

2.3 Study interventions

2.3.1 Randomisation

Randomisation is via a central internet-based system, stratified by site, recanalisation time from onset (<6, ≥6 hours), neurological impairment on the National Institutes for Health Stroke Scale (NIHSS) at admission (score <17 vs ≥17). A minimisation algorithm is used to ensure balance across stratification factors.

2.3.2 Study treatment

Intensive BP lowering group: to commence intravenous BP lowering therapy immediately after randomisation to the intervention group. The SBP target is <120 mmHg within 1 hour, and to maintain this level for at least 72 hours (or hospital discharge, if earlier).

Control group: the patient allocated to this group will receive a higher BP target strategy to maintain SBP level 140-180 mmHg after the EVT procedure. BP lowering treatment can be given only for a SBP level >150 mmHg, if required to achieve the target of ≥140 mmHg.

2.4 Outcomes

2.4.1 Primary outcome

- mRS at 90 days after randomisation analysed as an ordinal outcome

2.4.2 Secondary outcomes

- Intracerebral haemorrhage (ICH), assessed by CT imaging and adjudicated centrally according to five possible definitions:
    a) symptomatic ICH (sICH), based on National Institutes of Neurological Diseases and Stroke (NINDS)[2] criteria of brain imaging (or necropsy) confirmed ICH with ≥1 points deterioration in NIHSS score or death within 36 hours from baseline
    b) sICH, defined by Safe Implementation of Thrombolysis in Stroke-Monitoring Study (SITS-MOST)[3] criteria, as large ('type II') parenchymal ICH with ≥4 points decline in NIHSS score or death within 36 hours from baseline
    c) sICH, defined by the new Heidelberg Bleeding Classification (HBC) criteria,[4] the details of which are outlined in Appendix 1. *This will be the primary safety measure.*
    d) ICH of any type in brain imaging ≤7 days of treatment

e) any sICH after EVT within 90 days

- Imaging outcomes
  a) infarct size assessed by any form of brain imaging (MRI or CT) at 48±24 hours
  b) oedema size assessed by MRI or by CT during days 2-7
- Death or dependency, measured by NIHSS at 7 days
- The followings at 90 days:
  - Death or major disability (mRS 0-2 vs mRS 3-6)
  - Death and disability as separate categories (mRS 0-2 vs mRS 3-5 vs mRS 6)
  - Health-related quality of life (HRQoL) using EuroQoL EQ-5D-3L scale
  - Duration of hospitalisation
  - Residence
  - Hospital service cost (part of separate health economic analysis)

2.5 Sample size

The study is designed with 90% power to detect an odds ratio (OR) of 0.77 at 90 days between randomised groups in AIS patients with successful post-EVT reperfusion using an ordinal logistic regression. Assuming the distribution of mRS in the control group is 10.0%, 16.9%, 19.1%, 16.9%, 15.6%, 6.2%, and 15.3%, for scores of 0 to 6, respectively, this would correspond to a 6.48% absolute decrease in the proportion of patients experiencing a bad outcome (mRS 3-6), from 54% down to 47.52%, according to the results of the meta-analysis made by Efficacy of Endovascular Thrombectomy in Patients with M2 Segment Middle Cerebral Artery Occlusions (HERMES) collaboration.[5] This would translate into a 12% relative risk reduction (relative risk 0.88). A sample size of 2257 subjects is required to demonstrate this treatment effect, with 90% power and 4.82% type-1 error, where the Haybittle-Peto boundaries were used and taking into account 2 interim analyses during the study period.[6] The sample size allows for 5% lost to follow-up and 5% drop-in/drop-out.

3 Statistical analysis

3.1 Statistical principles

3.1.1 Level of statistical significance

The study includes two formal interim analysis after approximately one third and two thirds of patients have completed their 90-day follow-up, using the Haybittle-Peto stopping rule (3 standard-deviations) for efficacy.[6] To account for these two interim analyses, the significance threshold will be set at 4.82% for the final analysis. In case the trial is stopped early, the significance threshold will be adjusted accordingly, to account for the amount of 'alpha' spent.

Final analysis of the primary outcome, including sensitivity analyses, will all be conducted using a two-sided significance level of 4.82%.

For the 7 secondary clinical outcomes ([1] death or dependency at 7 days, and the following at 90 days: [2] death or major disability, [3] death, [4] disability, [5] HRQoL, [6] Duration of hospitalisation and [7] residence), the family-wise error rate will be controlled by applying a sequential Holm-Sidak correction.[7] Briefly, the approach consists of ordering all p values from smallest to largest, and then comparing them to an adjusted level of significance calculated as $1-(1-0.05)^{1/C}$, where C indicates the number of comparisons that remain. In the case of seven 7 secondary outcomes, the smallest p value would be compared to $1-(1-0.05)^{1/7}$, the second p value to $1-(1-0.05)^{1/6}$, and so on, with the last one being compared to 1-(1-0.05) (i.e. 0.05). The sequential testing procedure stops as soon as a p value fails to reach the corrected significance level. This will apply only to the primary analysis of the secondary outcomes (i.e. not to the adjusted models). For HRQoL, it will only apply to the analysis of the overall score. For ICH outcomes, the Heidelberg Bleeding Classification (HBC) criteria will be considered the primary measure with other definitions considered supportive. No multiplicity adjustment will be applied to the two imaging outcomes (infarct and oedema size) which are considered intermediary mechanistic outcomes.

3.1.2 Software

Analyses will be conducted primarily using SAS Enterprise Guide (version 9.3 or above) and R (version 4.0.0 or above).

3.2 Data sets analysed

Intention-to-treat (ITT) population: The ITT population will consist of all patients randomised regardless of whether they received the allocated intervention. This will be used as the basis to assess both efficacy and safety.

Efficacy analysis set: The main analysis set will consist of all patients in the ITT population with a non-missing primary outcome (i.e. those who are known to have died or with mRS cores at 90 days). In case of missing data leading to exclusion from the ITT population, sensitivity analyses will be performed (see Section 3.7.4).

Per-protocol (PP) analysis set: The PP set will consist of patients from the efficacy analysis who did not have a relevant protocol violation, defined as any of: age <18 years; final diagnosis not AIS; SBP <140 mmHg (inclusion criteria BP level); EVT undertaken >24 hours; EVT did not achieve reperfusion (eTICI score <2b); and failure to obtain a blind assessment of the 90-day outcome. The per-protocol set will be applied as a sensitivity analysis.

3.3 Subject disposition

The flow of patients through the trial will be displayed in a CONSORT[8] (Consolidated Standards of Reporting Trials) diagram. The report will include the following: the number of screened patients who met study inclusion criteria and the number of patients who were included; and reasons for exclusion of non-included patients.

3.4 Patient characteristics and baseline comparisons

Description of the baseline characteristics will be presented by treatment group as outlined in Appendix 1 (Table 1). Discrete variables will be summarised by frequencies and percentages. Percentages will be calculated according to the number of patients for whom data are available. Continuous variables will be summarised using mean and SD, and median and interquartile range (IRQ, Q1-Q3). Baseline measures will include all socio-demographic, clinical and medical information, collected at baseline; some of these data will be defined after the results of investigations have been completed (e.g. final pathological diagnosis) or central adjudication of the brain and vascular imaging (e.g. site and degree of LVO, and grading of collateral vessel status).

3.5 Process measures of background management and treatment

All assessments performed and interventions received between Day 1 and Day 7 will be described by intervention group. No formal statistical tests are planned for these variables.

Protocol deviations will be categorised and reported as the number and proportion of subjects experiencing a deviation. A listing of all protocol deviations will be provided.

3.6 BP management

BP measurements collected during the first 24 hours will be summarised using descriptive and longitudinal mean plots. The overall mean per treatment arm, and overall difference (and 95% confidence interval [CI]) between treatment arms, will be calculated using a repeated-measure linear mixed model with a fixed effect of treatment, a fixed categorical effect of time, a fixed interaction between treatment and time, and a repeated patient effect (to model within-patient correlations assuming a compound-symmetry structure). We will adjust for stratification variables by including a random site effect, a fixed effect for time from onset to recanalisation (<6 vs ≥ 6 hours), and a fixed effect for baseline NIHSS (<17 vs ≥ 17). Estimates will be weighted to reflect the unequal spacing between measurements.

BP lowering medications administered during the first 24 hours, and during days 2-7, will be described as the number and proportion of participants receiving each medication. This will include method of intravenous (iv) administration as well as the number of different iv or oral medications (0, 1, 2, ≥3) taken. No statistical test will be performed.

3.7 Analysis of the primary outcome

The primary outcome of the mRS at 90 days will be analysed as an ordinal variable with 7 levels. The primary intervention effect will be estimated as the OR of a higher mRS between the intervention arm and the control arm obtained from an ordinal logistic model (defined below).

3.7.1 Main analysis

To account for stratification by site and to maximise power,[9] the main analysis will be performed using ordinal logistic regression with treatment allocation as a fixed effect, site as a random effect,[10] and time from onset and baseline NIHSS as fixed covariates. The effect of the intervention will be presented as the OR of a worse outcome and its 95% CI using the control arm as the reference (i.e., where an OR greater than unity corresponds to an increase in mRS in the intervention arm compared to the control arm).

We will test the proportional-odds assumption using a score test. In case of violation, we will still proceed with the analysis and interpret the intervention OR as an average effect across all mRS levels but with the understanding that it may not be constant across all levels. This will be complemented by a graphical assessment of shifts across categories using bar plots as well as a binary analysis (see Section 3.8.1). As a sensitivity analysis, we will apply partial proportional odds logistic regression, relaxing the proportional odds assumption for covariates where it does not hold.

3.7.2 Adjusted analyses

Adjusted analyses will be performed by adding the following covariates to the main ordinal logistic regression model: country of recruitment (if multiple countries), mRS before stroke (categorical), age (continuous), sex (male vs female). The adjusted treatment effect will be reported as the adjusted OR and 95% CI. As for the main analysis, in case of violation of the proportional odds assumption, we will perform both a full proportional odds model as well as a partial proportional odds model for covariates violating the assumption.

3.7.3 Subgroup analyses

Ten pre-specified subgroup analyses will be carried out, irrespective of whether there is a significant treatment effect on the primary outcome. Subgroups are defined as follows:

- Age (<65 vs 65 or more)
- Sex (male vs female)
- Onset time to recanalisation (<6 vs ≥6 hours)
- Baseline systolic and diastolic BP (above vs below median)
- History of hypertension (yes vs no)
- Ethnicity (Asian vs other), only if recruitment outside of China

- Presumed aetiological subtype (intracranial atherosclerosis vs extracranial atherosclerosis vs cardioembolism vs dissection/other)
- Bassline NIHSS (above vs below median)
- TICI score after EVT (2b vs 3)
- Occlusion site (anterior circulation vs. posterior circulation)
- IV thrombolysis administered (yes vs no)

The analysis for each subgroup will be performed by adding the subgroup variable as well as its interaction with the intervention as fixed effects to the main logistic regression model (see Section 3.7.1). Within each subgroup, summary measures will include raw counts and percentages within each treatment arm, as well as the OR for treatment effect with a 95% CI. The results will be displayed on a forest plot, including the p-value for heterogeneity corresponding to the interaction term between the intervention and subgroup variable.

3.7.4 Treatment of missing data

The proportion of data missing for the primary outcome (mRS at 90 days) will be described while blinded to the intervention. In case of non-negligible amounts of missing data (>5%), we will use controlled multiple imputations to assess under what conditions the results change, and how plausible these conditions are, using the approach described by Cro et al.[11]

We will first run an imputation model under the missing at random (MAR) assumption. This MAR imputation model will use fully conditional specification (FCS)[12] and will include the following variables: mRS at 90 days, the NIHSS at 7 days (or hospital discharge, if sooner), a variable indicating the intervention, and all key socio-demographic, clinical, and medical baseline variables. The mRS at 7 or 90 days and NIHSS at 7 days will be imputed using an ordinal logistic model. Other variables will be imputed using either linear regression (for continuous/ordinal variables) or a discriminant function method (for nominal variables). One hundred sets of imputed data will be created and analysed using the model described in Section 3.7.1. Estimates of the treatment effect (e^{θ} in Model 1) and its standard errors will be combined to obtain a pooled common OR and 95%CI.

Using the same 100 sets of imputed data as our base, we will then assume different mRS levels for subjects who had missing mRS data at 90 days and had their mRS value imputed. We will assume that those with a missing mRS were more likely to have a poorer outcome than those with a non-missing mRS; we will therefore add 1 to their imputed mRS score (with a maximum score of 6 for those with no vital status available or a maximum score of 5 for those known to be alive). We will then analyse the 100 modified-imputed dataset and combine the results using the same strategy as for the base set of imputed data. As an additional sensitivity analysis, we will impute all missing mRS score at 90 days with the worst possible score (i.e. a score of 6 for those with unknown vital status and a score of 5 for those known to be alive but with a missing mRS).

While this assumption is unlikely to hold in most cases, it is plausible that some subjects may have become uncontactable due to death or serious deterioration after hospital discharge.

3.7.5 Per-protocol analyses

The main model (section 3.7.1) as well as the adjusted analyses (section 3.7.2) will be repeated in the PP population as defined in Section 3.2.

3.8 Analysis of secondary outcomes

All secondary outcome analyses described in this section will be performed in the efficacy (primary) and PP (sensitivity) analyses sets as defined in Section 3.2.

3.8.1 Binary analyses of mRS

A binary analysis of the mRS at 3 months will be performed by dichotomising the mRS as either 'poor' (scores 3-6) or 'favourable' (scores 0-2) outcomes. This analysis will be conducted using an unadjusted random-effect logistic regression that is similar to Model 1 (see Section 3.7.1), but this time with a binomial outcome and a logit link function. The effect of the intervention will be presented as the OR of a poor outcome with associated 95% CI. We will also apply the covariate adjustments described in Section 3.7.2; however, no subgroup or imputed analysis will be performed on this outcome. A similar analysis will be performed on mortality alone (mRS of 6 vs 0-5) and on dependency alone (mRS 3-5 vs 0-2). For dependency alone, the analysis will be restricted to subjects who are alive at 90 days (mRS 0-5).

3.8.2 ICH outcomes

ICH is defined according to 5 definitions (see Section 2.4.2) but the primary measure will be with the Heidelberg criteria. These will be reported as the number and proportion of subjects experiencing an event. The effect of the intervention will be estimated using the same approach as in the binary analysis of mRS (see Section 3.8.1). We will apply the covariate adjustments described in Section 3.7.2; however, no subgroup or imputed analysis will be performed on this outcome.

3.8.3 NIHSS score at 7 days

The NIHSS score at 7 days will be categorised into 7 levels (<5, 5-9, 10-14, 15-19, 20-24, ≥25, and death), and analysed using the same method as the mRS score described in Section 3.7.1. As a sensitivity analysis, the NIHSS score will also be analysed as a continuous variable using an unadjusted hierarchal linear regression model that is similar to Model 1, but assuming a normal distribution and an identity link function. The effect of the intervention will be presented as the mean difference and associated 95%CI. The covariate adjustments described in Section 3.7.2 will also be applied; however, no subgroup or imputed analysis will be performed on this outcome.

3.8.4 Imaging endpoints

Infarct and oedema size will be analysed using linear mixed models with the same fixed and random effects as the main outcome analysis. Given that baseline measurements may not be available for all patients, we will use a constrained longitudinal data analysis (cLDA) model[13] with both the baseline value and the follow-up value included as outcomes. The cLDa model constraints the mean baseline values to be equal between the two arms, which is a plausible assumption in a randomised trial. This approach has the advantage that any patient with at least one measurement (baseline or follow-up) can be included in the analysis instead of discarding patients with a missing baseline measurement. The effect of the intervention will be estimated as the mean difference and 95%CI at the follow-up time.

3.8.5 HRQoL

Each of the 5 EQ-5D dimensions will be analysed via ordinal logistic regression using the same model as for the primary analysis of mRS at 90 days (Section 3.7.1). The visual analogous scale (score of 0 to 100) will be analysed using the same approach but with linear regression (i.e. assuming a normal distribution and an identity link function). We do not plan adjusted or subgroup analyses. Further analysis of EQ-5D will be undertaken as part of an economic evaluation, which is outside the scope of this SAP.

3.8.6 Duration of hospitalisation

Duration of hospitalisation will be analysed as the time to discharge censored at 90 days or when the subject was last known to be alive and in hospital, whichever is earlier. It will be summarised using cumulative incidence functions treating mortality as a competing risk. Medians and quartiles of time to discharge will be obtained from the cumulative incidence functions. The effect of the intervention will be estimated as the hazard ratio (intervention divided by control) and its 95%CI obtained from a Cox model of the cause-specific hazard, which estimates the risk of discharge in subjects who are still alive and have not yet been discharged.[14] Fixed effects will include the intervention and the stratification variables (time from onset and baseline NIHSS). Site will be adjusted for using a shared-parameter frailty Cox model with a random site effect.[15] No adjusted or subgroup analyses are planned.

3.8.7 Residence

The patient's place of residence at 90 days will be analysed as a binary outcome using the same approach as for the binary analysis of the mRS at 90 days (Section 3.8.1). For the purpose of the model, residence will be defined as follows:

(1) home: own home (independent or with assistance) or family member's home

(2) institution: hospital, care facility or other

No adjusted or subgroup analyses are planned.

3.8.8 Serious adverse events (SAEs)

SAEs will be summarised as the number of events as well as the number and proportion of patients experiencing at least one SAE event. This will be done overall and by category of event according to Medical Dictionary for Regulatory Activities (MeDRA) system organ classes and preferred terms. The overall proportion of patients with SAEs in the intervention and control arms will be compared using logistic regression as in the binary analysis of mRS (see Section 3.8.1). Primary and underlying causes of deaths will be summarised by treatment arm with no formal test.

3.9 Analysis of substudies

The main purpose of the substudies is to define recruitment, safety and adherence to the protocol, to inform the feasibility of future confirmatory studies.

Description of the baseline characteristics will be presented by treatment group. Discrete variables will be summarised by frequencies and percentages. Percentages will be calculated according to the number of patients for whom data are available. Continuous variables will be summarised using mean and SD, and median and IQR. Baseline measures will include all socio-demographic, clinical and medical information, collected at baseline.

The main outcomes will be recurrent ischaemic stroke, ICH, death, and any SAE over 12 months. These data will be reported as the number and proportion of subjects experiencing an event. The effect of the intervention will be estimated using the same approach as in the binary analysis of mRS (see Section 3.8.1). We will apply the covariate adjustments described in Section 3.7.2; however, no subgroup or imputed analysis will be performed on this outcome.

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Appendix 1: Scales

1. The thrombolysis in cerebral infarction (TICI) grading system

The TICI system was described in 2003 by Higashida et al.[16] as a tool for determining the response of thrombolytic therapy for acute ischaemic stroke. In neurointerventional radiology it is commonly used for patients post-endovascular revascularisation. Like most therapy response grading systems, it predicts prognosis.

The original description was based on the angiographic appearances of the treated occluded vessel and the distal branches:

- Grade 0: no perfusion
- Grade 1: penetration with minimal perfusion
- Grade 2: partial perfusion
    - Grade 2a: only partial filling (less than two-thirds) of the entire vascular territory is visualised
    - Grade 2b: complete filling of all of the expected vascular territory is visualised but the filling is slower than normal
- Grade 3: complete perfusion

A consensus paper from three collaborative groups published in Stroke in 2013[17] recommended a modified scale, and a change of name to the modified Treatment in Cerebral Infarction (mTICI), to better reflect the increased use of endovascular therapies. Essentially, there was simplification of the TICI 2 component to less than half of the target vascular territory (mTICI 2a) or more than half (mTICI 2b).

Classification

- grade 0: no perfusion
- grade 1: antegrade reperfusion past the initial occlusion, but limited distal branch filling with little or slow distal reperfusion
- grade 2
    - grade 2a: antegrade reperfusion of less than half of the occluded target artery previously ischaemic territory (e.g. in one major division of the middle cerebral artery (MCA) and its territory)
    - grade 2b: antegrade reperfusion of more than half of the previously occluded target artery ischaemic territory (e.g. in two major divisions of the MCA and their territories)
- grade 3: complete antegrade reperfusion of the previously occluded target artery ischaemic territory, with absence of visualised occlusion in all distal branches

The **expanded treatment in cerebral infarction (eTICI**) **score** is a further modification of the mTICI and TICI scales, published by the HERMES investigators in 2019.[18] Using mRS shift analysis as the outcome measure, the investigators found a significant difference in outcomes for patients with partial recanalisation after EVT between those with reperfusion of 50-66%, 67-89% and 90-90%, in addition to those previously defined by mTICI.

Classification

- grade 0: no perfusion noted (0% reperfusion)
- grade 1: reduction in thrombus but without any resultant filling of distal arterial branches
- grade 2
    - grade 2a: reperfusion of 1-49% of the territory

- grade 2b50: reperfusion of 50–66% of the territory
- grade 2b67: reperfusion of 67–89% of the territory
- grade 2c: extensive reperfusion of 90–99% of the territory

- grade 3: complete or full reperfusion (100% reperfusion)

2. Heidelberg bleeding classification

Class 1: haemorrhagic transformation of infarcted brain tissue

1a: HT1: scattered small petechiae, no mass effect

1b: HT2: confluent petechia, no mass effect

1c: PT1: haematoma within infarcted tissue, occupying <30%, no substantive mass effect:

Class 2: intracerebral haemorrhage within and beyond infarcted tissue

PH2: haematoma occupying ≥30% of the infarcted tissue with obvious mass effect

Class 3: intracerebral haemorrhage outside the infarcted brain tissue or intracranial-extracranial haemorrhage

3a: parenchymal haematoma remote from infarcted tissue

3b: intraventricular haemorrhage

3c: subarachnoid haemorrhage

3d: subdural haemorrhage

Symptomatic haemorrhages are considered definite if any intracranial haemorrhage is the dominant brain pathology on imaging causal for deterioration. However, in some cases, the causality is not certain because the ischaemic infarct may have contributed to the deterioration, so the following classification is applied for reporting of trials:

Symptomatic

probable relatedness: class 2 (PH2) haemorrhage

Asymptomatic

Possibly relatedness: class 1b (HT2), 1c (PH1) and 3 haemorrhages

Unlikely relatedness: class 1a (HT1) haemorrhage

Relatedness to intervention is further specified following reperfusion therapy:

Definite: observed procedural complication

Probable: treatment within 24 hours and class 1c or 2 hemorrhage (PH) (symptomatic or asymptomatic)

Possible: treatment within 24 hours and class 1a or 1b haemorrhage (HI) (symptomatic or asymptomatic)

Unrelated: no intervention in the 24 hours prior to haemorrhage detection

Appendix 2: Proposed Tables and figures

4.1 Tables

Table 1. Baseline characteristics

	Intensive BP lowering (N =)	Guideline-recommended BP lowering (N =)	Total (N =)
Age (years)	xxx	xxx	xxx
Mean (SD)	xxx.x (xxx.x)	xxx.x (xxx.x)	xxx.x (xxx.x)
Median (Q1; Q3)	xxx (xxx; xxx)	xxx (xxx; xxx)	xxx (xxx; xxx)
min max	xxx to xxx	xxx to xxx	xxx to xxx
Sex	xxx	xxx	xxx
Male	xxx xx.x%	xxx xx.x%	xxx xx.x%
Female	xxx xx.x%	xxx xx.x%	xxx xx.x%
Ethnicity	xxx	xxx	xxx
Chinese	xxx xx.x%	xxx xx.x%	xxx xx.x%
Caucasian/European	xxx xx.x%	xxx xx.x%	xxx xx.x%
Other	xxx xx.x%	xxx xx.x%	xxx xx.x%
Systolic Blood Pressure (mmHg) on arrival	xxx	xxx	xxx
Mean (SD)	xxx.x (xxx.x)	xxx.x (xxx.x)	xxx.x (xxx.x)
Median (Q1; Q3)	xxx (xxx; xxx)	xxx (xxx; xxx)	xxx (xxx; xxx)
min max	xxx to xxx	xxx to xxx	xxx to xxx
Diastolic Blood Pressure (mmHg) on arrival	xxx	xxx	xxx
Mean (SD)	xxx.x (xxx.x)	xxx.x (xxx.x)	xxx.x (xxx.x)
Median (Q1; Q3)	xxx (xxx; xxx)	xxx (xxx; xxx)	xxx (xxx; xxx)
min max	xxx to xxx	xxx to xxx	xxx to xxx
Heart Rate (bpm)	xxx	xxx	xxx
Mean (SD)	xxx.x (xxx.x)	xxx.x (xxx.x)	xxx.x (xxx.x)
Median (Q1; Q3)	xxx (xxx; xxx)	xxx (xxx; xxx)	xxx (xxx; xxx)
min max	xxx to xxx	xxx to xxx	xxx to xxx
Blood Glucose (mmol/L)	xxx	xxx	xxx
Mean (SD)	xxx.x (xxx.x)	xxx.x (xxx.x)	xxx.x (xxx.x)

	Intensive BP lowering (N =)	Guideline-recommended BP lowering (N =)	Total (N =)
Median (Q1; Q3)	xxx (xxx; xxx)	xxx (xxx; xxx)	xxx (xxx; xxx)
min max	xxx to xxx	xxx to xxx	xxx to xxx
Pre-stroke modified Rankin scale	xxx	xxx	xxx
0 - no symptoms	xxx xx.x%	xxx xx.x%	xxx xx.x%
1 - no significant disability (with symptoms)	xxx xx.x%	xxx xx.x%	xxx xx.x%
2 - slight disability (but independent in daily activities)	xxx xx.x%	xxx xx.x%	xxx xx.x%
3 - moderate disability (requiring some help from another person for daily activities)	xxx xx.x%	xxx xx.x%	xxx xx.x%
4 - moderate severe disability (requiring regular help from another person)	xxx xx.x%	xxx xx.x%	xxx xx.x%
5 - severe disability (bed bound, totally dependent)	xxx xx.x%	xxx xx.x%	xxx xx.x%
NIHSS Score on arrival	xxx	xxx	xxx
Mean (SD)	xxx.x (xxx.x)	xxx.x (xxx.x)	xxx.x (xxx.x)
Median (Q1; Q3)	xxx (xxx; xxx)	xxx (xxx; xxx)	xxx (xxx; xxx)
min max	xxx to xxx	xxx to xxx	xxx to xxx
GCS Score on arrival	xxx	xxx	xxx
Mean (SD)	xxx.x (xxx.x)	xxx.x (xxx.x)	xxx.x (xxx.x)
Median (Q1; Q3)	xxx (xxx; xxx)	xxx (xxx; xxx)	xxx (xxx; xxx)
min max	xxx to xxx	xxx to xxx	xxx to xxx
Eyes Open	xxx	xxx	xxx
1=none	xxx xx.x%	xxx xx.x%	xxx xx.x%
2=To pain	xxx xx.x%	xxx xx.x%	xxx xx.x%
3=To speech	xxx xx.x%	xxx xx.x%	xxx xx.x%
4=Spontaneously	xxx xx.x%	xxx xx.x%	xxx xx.x%
Verbal Response	xxx	xxx	xxx
1=none	xxx xx.x%	xxx xx.x%	xxx xx.x%
2=Incomprehensible sounds	xxx xx.x%	xxx xx.x%	xxx xx.x%
3=Inappropriate words	xxx xx.x%	xxx xx.x%	xxx xx.x%
4=Confused	xxx xx.x%	xxx xx.x%	xxx xx.x%
5=Orientated	xxx xx.x%	xxx xx.x%	xxx xx.x%
Motor Response	xxx	xxx	xxx

	Intensive BP lowering (N =)	Guideline-recommended BP lowering (N =)	Total (N =)
1=none	xxx xx.x%	xxx xx.x%	xxx xx.x%
2=Extension to pain	xxx xx.x%	xxx xx.x%	xxx xx.x%
3=Flexion to pain	xxx xx.x%	xxx xx.x%	xxx xx.x%
4=Withdraws	xxx xx.x%	xxx xx.x%	xxx xx.x%
5=Localises to pain	xxx xx.x%	xxx xx.x%	xxx xx.x%
6=Obey commands	xxx xx.x%	xxx xx.x%	xxx xx.x%
Time from onset to diagnostic CT	xxx	xxx	xxx
Mean (SD)	xxx.x (xxx.x)	xxx.x (xxx.x)	xxx.x (xxx.x)
Median (Q1; Q3)	xxx (xxx; xxx)	xxx (xxx; xxx)	xxx (xxx; xxx)
min max	xxx to xxx	xxx to xxx	xxx to xxx
Time from onset to diagnostic MRI	xxx	xxx	xxx
Mean (SD)	xxx.x (xxx.x)	xxx.x (xxx.x)	xxx.x (xxx.x)
Median (Q1; Q3)	xxx (xxx; xxx)	xxx (xxx; xxx)	xxx (xxx; xxx)
min max	xxx to xxx	xxx to xxx	xxx to xxx
Time from onset to groin puncture	xxx	xxx	xxx
Mean (SD)	xxx.x (xxx.x)	xxx.x (xxx.x)	xxx.x (xxx.x)
Median (Q1; Q3)	xxx (xxx; xxx)	xxx (xxx; xxx)	xxx (xxx; xxx)
min max	xxx to xxx	xxx to xxx	xxx to xxx
Time from groin puncture to recanalisation	xxx	xxx	xxx
Mean (SD)	xxx.x (xxx.x)	xxx.x (xxx.x)	xxx.x (xxx.x)
Median (Q1; Q3)	xxx (xxx; xxx)	xxx (xxx; xxx)	xxx (xxx; xxx)
min max	xxx to xxx	xxx to xxx	xxx to xxx
Time from recanalisation to randomisation	xxx	xxx	xxx
Mean (SD)	xxx.x (xxx.x)	xxx.x (xxx.x)	xxx.x (xxx.x)
Median (Q1; Q3)	xxx (xxx; xxx)	xxx (xxx; xxx)	xxx (xxx; xxx)
min max	xxx to xxx	xxx to xxx	xxx to xxx
Time from onset to randomisation	xxx	xxx	xxx
Mean (SD)	xxx.x (xxx.x)	xxx.x (xxx.x)	xxx.x (xxx.x)
Median (Q1; Q3)	xxx (xxx; xxx)	xxx (xxx; xxx)	xxx (xxx; xxx)
min max	xxx to xxx	xxx to xxx	xxx to xxx

	Intensive BP lowering (N =)	Guideline-recommended BP lowering (N =)	Total (N =)
Systolic blood pressure after recanalisation	xxx	xxx	xxx
Mean (SD)	xxx.x (xxx.x)	xxx.x (xxx.x)	xxx.x (xxx.x)
Median (Q1; Q3)	xxx (xxx; xxx)	xxx (xxx; xxx)	xxx (xxx; xxx)
min max	xxx to xxx	xxx to xxx	xxx to xxx
Diastolic blood pressure after recanalisation	xxx	xxx	xxx
Mean (SD)	xxx.x (xxx.x)	xxx.x (xxx.x)	xxx.x (xxx.x)
Median (Q1; Q3)	xxx (xxx; xxx)	xxx (xxx; xxx)	xxx (xxx; xxx)
min max	xxx to xxx	xxx to xxx	xxx to xxx
IV thrombolysis administered	xxx	xxx	xxx
yes	xxx xx.x%	xxx xx.x%	xxx xx.x%
no	xxx xx.x%	xxx xx.x%	xxx xx.x%
Brain imaging features			
CT performed	xxx xx.x%	xxx xx.x%	xxx xx.x%
MRI performed	xxx xx.x%	xxx xx.x%	xxx xx.x%
Visible early ischaemic changes	xxx xx.x%	xxx xx.x%	xxx xx.x%
Visible cerebral infarction lesion	xxx xx.x%	xxx xx.x%	xxx xx.x%
Visible cerebral infarction with mass effect	xxx xx.x%	xxx xx.x%	xxx xx.x%
Volume of infarct core (RAPID software)	xxx	xxx	xxx
Mean (SD)	xxx.x (xxx.x)	xxx.x (xxx.x)	xxx.x (xxx.x)
Median (Q1; Q3)	xxx (xxx; xxx)	xxx (xxx; xxx)	xxx (xxx; xxx)
min max	xxx to xxx	xxx to xxx	xxx to xxx
Volume of perfusion lesion			
Mean (SD)	xxx.x (xxx.x)	xxx.x (xxx.x)	xxx.x (xxx.x)
Median (Q1; Q3)	xxx (xxx; xxx)	xxx (xxx; xxx)	xxx (xxx; xxx)
min max	xxx to xxx	xxx to xxx	xxx to xxx
Mismatch volume	xxx	xxx	xxx
Mean (SD)	xxx.x (xxx.x)	xxx.x (xxx.x)	xxx.x (xxx.x)
Median (Q1; Q3)	xxx (xxx; xxx)	xxx (xxx; xxx)	xxx (xxx; xxx)
min max	xxx to xxx	xxx to xxx	xxx to xxx

	Intensive BP lowering (N =)	Guideline-recommended BP lowering (N =)	Total (N =)
Occlusion cerebral vessel site	xxx	xxx	xxx
ACA	xxx xx.x%	xxx xx.x%	xxx xx.x%
M1 MCA	xxx xx.x%	xxx xx.x%	xxx xx.x%
M2 MCA	xxx xx.x%	xxx xx.x%	xxx xx.x%
TICA	xxx xx.x%	xxx xx.x%	xxx xx.x%
Proximal ICA	xxx xx.x%	xxx xx.x%	xxx xx.x%
PCA	xxx xx.x%	xxx xx.x%	xxx xx.x%
VA	xxx xx.x%	xxx xx.x%	xxx xx.x%
BA	xxx xx.x%	xxx xx.x%	xxx xx.x%
eTICI score before EVT	xxx	xxx	xxx
0	xxx xx.x%	xxx xx.x%	xxx xx.x%
I	xxx xx.x%	xxx xx.x%	xxx xx.x%
IIa	xxx xx.x%	xxx xx.x%	xxx xx.x%
IIb	xxx xx.x%	xxx xx.x%	xxx xx.x%
IIc	xxx xx.x%	xxx xx.x%	xxx xx.x%
III	xxx xx.x%	xxx xx.x%	xxx xx.x%
EVT details			
Anesthesia used	xxx xx.x%	xxx xx.x%	xxx xx.x%
General	xxx xx.x%	xxx xx.x%	xxx xx.x%
Conscious sedation	xxx xx.x%	xxx xx.x%	xxx xx.x%
Type of device used			
Stent retriever	xxx xx.x%	xxx xx.x%	xxx xx.x%
Aspiration catheter	xxx xx.x%	xxx xx.x%	xxx xx.x%
Balloon guide catheter	xxx xx.x%	xxx xx.x%	xxx xx.x%
Angioplasty	xxx xx.x%	xxx xx.x%	xxx xx.x%
Other	xxx xx.x%	xxx xx.x%	xxx xx.x%
Use of antithrombotic drugs	xxx	xxx	xxx
Heparin	xxx xx.x%	xxx xx.x%	xxx xx.x%
Mean dose	xxx.x (xxx.x)	xxx.x (xxx.x)	xxx.x (xxx.x)
GPIIb/IIIa inhibitor	xxx xx.x%	xxx xx.x%	xxx xx.x%
Tirofibran	xxx xx.x%	xxx xx.x%	xxx xx.x%

	Intensive BP lowering (N =)	Guideline-recommended BP lowering (N =)	Total (N =)
Other	xxx xx.x%	xxx xx.x%	xxx xx.x%
Use of intra-arterial thrombolysis	xxx xx.x%	xxx xx.x%	xxx xx.x%
Number of retrieval attempts/passes			
1	xxx xx.x%	xxx xx.x%	xxx xx.x%
2	xxx xx.x%	xxx xx.x%	xxx xx.x%
3	xxx xx.x%	xxx xx.x%	xxx xx.x%
>3	xxx xx.x%	xxx xx.x%	xxx xx.x%
eTICI score after EVT	xxx	xxx	xxx
0	xxx xx.x%	xxx xx.x%	xxx xx.x%
I	xxx xx.x%	xxx xx.x%	xxx xx.x%
IIa	xxx xx.x%	xxx xx.x%	xxx xx.x%
IIb	xxx xx.x%	xxx xx.x%	xxx xx.x%
IIc	xxx xx.x%	xxx xx.x%	xxx xx.x%
III	xxx xx.x%	xxx xx.x%	xxx xx.x%
Final diagnosis	xxx	xxx	xxx
Intracranial atherosclerosis	xxx xx.x%	xxx xx.x%	xxx xx.x%
External atherosclerosis	xxx xx.x%	xxx xx.x%	xxx xx.x%
Cardioembolism (AF-related)	xxx xx.x%	xxx xx.x%	xxx xx.x%
Cardioembolism (valve or myocardium)	xxx xx.x%	xxx xx.x%	xxx xx.x%
Stroke due to dissection	xxx xx.x%	xxx xx.x%	xxx xx.x%
Stroke of uncertain aetiology	xxx xx.x%	xxx xx.x%	xxx xx.x%

Table 2. Medical history

Variable	Intensive blood pressure lowering (N =)	Guideline-recommended blood pressure lowering (N =)	Total (N =)
Previous ischaemic stroke	xxx/xxx xx.x%	xxx/xxx xx.x%	xxx/xxx xx.x%
Previous haemorrhagic stroke	xxx/xxx xx.x%	xxx/xxx xx.x%	xxx/xxx xx.x%
Previous stroke of unknown type	xxx/xxx xx.x%	xxx/xxx xx.x%	xxx/xxx xx.x%
History of coronary heart disease	xxx/xxx xx.x%	xxx/xxx xx.x%	xxx/xxx xx.x%
History of documented atrial fibrillation	xxx/xxx xx.x%	xxx/xxx xx.x%	xxx/xxx xx.x%
History of valvular heart disease	xxx/xxx xx.x%	xxx/xxx xx.x%	xxx/xxx xx.x%
Other heart disease (e.g. heart failure)	xxx/xxx xx.x%	xxx/xxx xx.x%	xxx/xxx xx.x%
History of hypertension	xxx/xxx xx.x%	xxx/xxx xx.x%	xxx/xxx xx.x%
Currently treated hypertension	xxx/xxx xx.x%	xxx/xxx xx.x%	xxx/xxx xx.x%
History of diabetes mellitus	xxx/xxx xx.x%	xxx/xxx xx.x%	xxx/xxx xx.x%
Known coagulation or other haematological disorder	xxx/xxx xx.x%	xxx/xxx xx.x%	xxx/xxx xx.x%
History of liver disease	xxx/xxx xx.x%	xxx/xxx xx.x%	xxx/xxx xx.x%
History of gastrointestinal or urinary bleeding	xxx/xxx xx.x%	xxx/xxx xx.x%	xxx/xxx xx.x%
History of hypercholesterolaemia	xxx/xxx xx.x%	xxx/xxx xx.x%	xxx/xxx xx.x%
Current smoker	xxx/xxx xx.x%	xxx/xxx xx.x%	xxx/xxx xx.x%

Table 3. Medications at time of admission

Variable	Intensive BP lowering (N =)	Standard BP lowering (N =)	Total (N =)
Antihypertension drugs used	xxx/xxx xx.x%	xxx/xxx xx.x%	xxx/xxx xx.x%
Type of antihypertension drugs used	xxxx	xxxx	xxxx
ACE or ARB	xxx xx.x%	xxx xx.x%	xxx xx.x%
Diuretic	xxx xx.x%	xxx xx.x%	xxx xx.x%
Calcium channel blocker	xxx xx.x%	xxx xx.x%	xxx xx.x%
Beta-blocker	xxx xx.x%	xxx xx.x%	xxx xx.x%
Other antihypertensive agent	xxx xx.x%	xxx xx.x%	xxx xx.x%
Anticoagulant agent used	xxx/xxx xx.x%	xxx/xxx xx.x%	xxx/xxx xx.x%
Type of anticoagulant agent	xxxx	xxxx	xxxx
Vitamin K antagonist (warfarin, neo-sintrom)	xxx xx.x%	xxx xx.x%	xxx xx.x%
New oral anticoagulant	xxx xx.x%	xxx xx.x%	xxx xx.x%
Apixaban	xxx xx.x%	xxx xx.x%	xxx xx.x%
Dabigaruan	xxx xx.x%	xxx xx.x%	xxx xx.x%
Edoxaban	xxx xx.x%	xxx xx.x%	xxx xx.x%
Rivaroxaban	xxx xx.x%	xxx xx.x%	xxx xx.x%
Other anticoagulant	xxx xx.x%	xxx xx.x%	xxx xx.x%
Antiplatelet agent used	xxx/xxx xx.x%	xxx/xxx xx.x%	xxx/xxx xx.x%
Detailed antiplatelet agent	xxxx	xxxx	xxxx
Aspirin	xxx xx.x%	xxx xx.x%	xxx xx.x%
Clopidogrel	xxx xx.x%	xxx xx.x%	xxx xx.x%
Cilostazol	xxx xx.x%	xxx xx.x%	xxx xx.x%
Dipyridamole	xxx xx.x%	xxx xx.x%	xxx xx.x%
Other antiplatelet agent	xxx xx.x%	xxx xx.x%	xxx xx.x%
Blood glucose lowering agents used	xxx/xxx xx.x%	xxx/xxx xx.x%	xxx/xxx xx.x%
Type of glucose lowering agents	xxxx	xxxx	xxxx
Oral agents	xxx xx.x%	xxx xx.x%	xxx xx.x%
Insulin	xxx xx.x%	xxx xx.x%	xxx xx.x%

Variable	Intensive BP lowering (N =)	Standard BP lowering (N =)	Total (N =)
Nitrates used	xxx/xxx xx.x%	xxx/xxx xx.x%	xxx/xxx xx.x%
Statin or other lipid lowering agent	xxx/xxx xx.x%	xxx/xxx xx.x%	xxx/xxx xx.x%

Table 4. Clinical and BP measures recorded during the first 24 hours

Variable	Intensive BP lowering (N =)	Standard BP lowering (N =)	Total (N =)
NIHSS Score at 24 hours	xxx	xxx	xxx
Mean (SD)	xxx.x (xxx.x)	xxx.x (xxx.x)	xxx.x (xxx.x)
Median (Q1; Q3)	xxx (xxx; xxx)	xxx (xxx; xxx)	xxx (xxx; xxx)
min max	xxx to xxx	xxx to xxx	xxx to xxx
GCS Score at 24 hours	xxx	xxx	xxx
Mean (SD)	xxx.x (xxx.x)	xxx.x (xxx.x)	xxx.x (xxx.x)
Median (Q1; Q3)	xxx (xxx; xxx)	xxx (xxx; xxx)	xxx (xxx; xxx)
min max	xxx to xxx	xxx to xxx	xxx to xxx
Highest SBP (mmHg)	xxx	xxx	xxx
Mean (SD)	xxx.x (xxx.x)	xxx.x (xxx.x)	xxx.x (xxx.x)
Median (Q1; Q3)	xxx (xxx; xxx)	xxx (xxx; xxx)	xxx (xxx; xxx)
min max	xxx to xxx	xxx to xxx	xxx to xxx
Highest DBP (mmHg)	xxx	xxx	xxx
Mean (SD)	xxx.x (xxx.x)	xxx.x (xxx.x)	xxx.x (xxx.x)
Median (Q1; Q3)	xxx (xxx; xxx)	xxx (xxx; xxx)	xxx (xxx; xxx)
min max	xxx to xxx	xxx to xxx	xxx to xxx
Lowest SBP (mmHg)	xxx	xxx	xxx
Mean (SD)	xxx.x (xxx.x)	xxx.x (xxx.x)	xxx.x (xxx.x)
Median (Q1; Q3)	xxx (xxx; xxx)	xxx (xxx; xxx)	xxx (xxx; xxx)
min max	xxx to xxx	xxx to xxx	xxx to xxx
Lowest DBP (mmHg)	xxx	xxx	xxx
Mean (SD)	xxx.x (xxx.x)	xxx.x (xxx.x)	xxx.x (xxx.x)
Median (Q1; Q3)	xxx (xxx; xxx)	xxx (xxx; xxx)	xxx (xxx; xxx)
min max	xxx to xxx	xxx to xxx	xxx to xxx

Table 5. Antihypertensive treatments administered during the first 24 hours

Variable	Intensive BP lowering (N =)	Guideline-recommended BP lowering (N =)	Total (N =)
Any BP medication taken	xxx/xxx xx.x%	xxx/xxx xx.x%	xxx/xxx xx.x%
IV hypertensive treatment	xxx/xxx xx.x%	xxx/xxx xx.x%	xxx/xxx xx.x%
Types of IV hypertensive treatment	xxx	xxx	xxx
Bolus	xxx xx.x%	xxx xx.x%	xxx xx.x%
Infusion	xxx xx.x%	xxx xx.x%	xxx xx.x%
Type of IV antihypertensive treatment	xxx	xxx	xxx
<treatment 1>	xxx xx.x%	xxx xx.x%	xxx xx.x%
<treatment 2>	xxx xx.x%	xxx xx.x%	xxx xx.x%
Etc. in decreasing order of frequency	xxx xx.x%	xxx xx.x%	xxx xx.x%

Table 6. Management care administered until Day 7

Variable	Intensive blood pressure lowering (N =)	Guideline-recommended blood pressure lowering (N =)	Total (N =)
Intubation and ventilation	xxx/xxx xx.x%	xxx/xxx xx.x%	xxx/xxx xx.x%
Fever	xxx/xxx xx.x%	xxx/xxx xx.x%	xxx/xxx xx.x%
Fever treated	xxx/xxx xx.x%	xxx/xxx xx.x%	xxx/xxx xx.x%
Assisted feeding	xxx/xxx xx.x%	xxx/xxx xx.x%	xxx/xxx xx.x%
Mobilised by physiotherapist/occupational therapist	xxx/xxx xx.x%	xxx/xxx xx.x%	xxx/xxx xx.x%
Compression stockings used	xxx/xxx xx.x%	xxx/xxx xx.x%	xxx/xxx xx.x%
Subcutaneous heparin or heparinoids administered	xxx/xxx xx.x%	xxx/xxx xx.x%	xxx/xxx xx.x%
Intravenous heparin administered	xxx/xxx xx.x%	xxx/xxx xx.x%	xxx/xxx xx.x%
Glycaemic control given	xxx/xxx xx.x%	xxx/xxx xx.x%	xxx/xxx xx.x%
Aspirin or other anti-platelet agent administered	xxx/xxx xx.x%	xxx/xxx xx.x%	xxx/xxx xx.x%
Mannitol used	xxx/xxx xx.x%	xxx/xxx xx.x%	xxx/xxx xx.x%
Intravenous traditional Chinese medicine administered	xxx/xxx xx.x%	xxx/xxx xx.x%	xxx/xxx xx.x%
Intravenous steroids administered	xxx/xxx xx.x%	xxx/xxx xx.x%	xxx/xxx xx.x%
Hemicraniectomy performed	xxx/xxx xx.x%	xxx/xxx xx.x%	xxx/xxx xx.x%
Acute Stroke Unit admission	xxx/xxx xx.x%	xxx/xxx xx.x%	xxx/xxx xx.x%
Intensive care unit admission	xxx/xxx xx.x%	xxx/xxx xx.x%	xxx/xxx xx.x%
Requirement for any form of renal dialysis	xxx/xxx xx.x%	xxx/xxx xx.x%	xxx/xxx xx.x%
Clinical decision made to withdraw 'active' care	xxx/xxx xx.x%	xxx/xxx xx.x%	xxx/xxx xx.x%
Rehabilitation therapy given	xxx/xxx xx.x%	xxx/xxx xx.x%	xxx/xxx xx.x%

Table 7. Details of hypertensive treatments between Days 2 and 7

Variable	Intensive BP lowering (N =)	Standard BP lowering (N =)	Total (N =)
IV antihypertensive treatment	xxx/xxx xx.x%	xxx/xxx xx.x%	xxx/xxx xx.x%
Type of IV antihypertensive treatment	xxx	xxx	xxx
<treatment 1>	xxx xx.x%	xxx xx.x%	xxx xx.x%
<treatment 2>	xxx xx.x%	xxx xx.x%	xxx xx.x%
Etc. in decreasing order of frequency	xxx xx.x%	xxx xx.x%	xxx xx.x%
Oral hypertensive treatment	xxx/xxx xx.x%	xxx/xxx xx.x%	xxx/xxx xx.x%
Type of oral antihypertensive treatment	xxx	xxx	xxx
<treatment 1>	xxx xx.x%	xxx xx.x%	xxx xx.x%
<treatment 2>	xxx xx.x%	xxx xx.x%	xxx xx.x%
Etc. in decreasing order of frequency	xxx xx.x%	xxx xx.x%	xxx xx.x%

Table 8. Descriptive analysis of blood pressure

Variable / Timepoint	Intensive BP lowering (N =)	Standard BP lowering (N =)	Total (N =)
SBP (n mean (SD)			
Randomisation	xxx xxx.x (xx.x)	xxx xxx.x (xx.x)	xxx xxx.x (xx.x)
15 min	xxx xxx.x (xx.x)	xxx xxx.x (xx.x)	xxx xxx.x (xx.x)
30 min	xxx xxx.x (xx.x)	xxx xxx.x (xx.x)	xxx xxx.x (xx.x)
45 min	xxx xxx.x (xx.x)	xxx xxx.x (xx.x)	xxx xxx.x (xx.x)
1 hr	xxx xxx.x (xx.x)	xxx xxx.x (xx.x)	xxx xxx.x (xx.x)
2 hr	xxx xxx.x (xx.x)	xxx xxx.x (xx.x)	xxx xxx.x (xx.x)
Etc.			
Day 7, pm	xxx xxx.x (xx.x)	xxx xxx.x (xx.x)	xxx xxx.x (xx.x)
DBP (n mean (SD))			
Randomisation	xxx xxx.x (xx.x)	xxx xxx.x (xx.x)	xxx xxx.x (xx.x)
15 min	xxx xxx.x (xx.x)	xxx xxx.x (xx.x)	xxx xxx.x (xx.x)
30 min	xxx xxx.x (xx.x)	xxx xxx.x (xx.x)	xxx xxx.x (xx.x)
45 min	xxx xxx.x (xx.x)	xxx xxx.x (xx.x)	xxx xxx.x (xx.x)
1 hr	xxx xxx.x (xx.x)	xxx xxx.x (xx.x)	xxx xxx.x (xx.x)
2 hr	xxx xxx.x (xx.x)	xxx xxx.x (xx.x)	xxx xxx.x (xx.x)
Etc.			
Day 7, pm	xxx xxx.x (xx.x)	xxx xxx.x (xx.x)	xxx xxx.x (xx.x)

Table 9. Descriptive analysis of mRS

Timepoint / Score	Intensive BP lowering (N =)	Standard BP lowering (N =)	Total (N =)
Baseline	N=xxx	N=xxx	N=xxx
0	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
1	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
2	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
3	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
4	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
5	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
6	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Day 7	N=xxx	N=xxx	N=xxx
0	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
1	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
2	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
3	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
4	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
5	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
6	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Day 90	N=xxx	N=xxx	N=xxx
0	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
1	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
2	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
3	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
4	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
5	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
6	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)

Table 10. Descriptive analysis of NIHSS

	Intensive BP lowering (N =)	Guideline-recommended BP lowering (N =)	Total (N =)
Baseline	N=xxx	N=xxx	N=xxx
< 5	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
5 – 9	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
10 – 14	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
15 – 19	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
20 – 24	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
≥ 25	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Death	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Mean (SD)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Median (Q1 – Q2)	xx (xx – xx)	xx (xx – xx)	xx (xx – xx)
Min - Max	xx – xx	xx – xx	xx – xx
Day 7	N=xxx	N=xxx	N=xxx
< 5	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
5 – 9	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
10 – 14	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
15 – 19	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
20 – 24	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
≥ 25	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Death	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Mean (SD)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Median (Q1 – Q2)	xx (xx – xx)	xx (xx – xx)	xx (xx – xx)
Min - Max	xx – xx	xx – xx	xx – xx

Table 11. Descriptive analysis of EQ-5D at 90 days

	Intensive BP lowering (N =)	Guideline-recommended BP lowering (N =)	Total (N =)
Mobility	N=xxx	N=xxx	N=xxx
No problems	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Some problems	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Confined to bed	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Self-care	N=xxx	N=xxx	N=xxx
No problems	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Some problems	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Unable to wash or dress	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Usual activities	N=xxx	N=xxx	N=xxx
No problems	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Some problems	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Unable to perform usual activities	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Pain / discomfort	N=xxx	N=xxx	N=xxx
No pain or discomfort	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Moderate pain or discomfort	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Extreme pain or discomfort	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Anxiety / depression	N=xxx	N=xxx	N=xxx
Not anxious or depressed	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Moderately anxious or depressed	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Extremely anxious or depressed	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
VAS (/100)	N=xxx	N=xxx	N=xxx
Mean (SD)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Median (Q1 – Q2)	xx (xx – xx)	xx (xx – xx)	xx (xx – xx)
Min - Max	xx – xx	xx – xx	xx – xx

Table 12. Imaging outcomes

Outcome	Raw data		Model results			
	Intensive BP Control N mean (SD)	Guideline BP Control N mean (SD)	Intensive BP Control Mean (SE)	Guideline BP Control Mean (SE)	Mean difference (95% CI)	P-value
Infarct size (mL)						
Baseline	xx xx.x (xx.xx)	xx xx.x (xx.xx)				
48 hours	xx xx.x (xx.xx)	xx xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)	xx.xx (xx.xx to xx.xx)	0.xxx
Oedema volume (mL)						
Baseline	xx xx.x (xx.xx)	xx xx.x (xx.xx)				
48 hours	xx xx.x (xx.xx)	xx xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)	xx.xx (xx.xx to xx.xx)	0.xxx

Programming notes:
- *repeat this table in the per-protocol population*

Table 13. Clinical outcomes: model results

Outcome / analysis method	Unadjusted model [1] N	Unadjusted model [1] OR/MD/HR (95% CI)	Unadjusted model [1] P-value	Adjusted model [2] N	Adjusted model [2] OR/MD/HR (95% CI)	Adjusted model [2] P-value
mRS at Day 90 (ordinal)						
Main, non-imputed model [3]	xxxx	xx.xx (xx.xx to xx.xx)	0.xxx	xxxx	xx.xx (xx.xx to xx.xx)	0.xxx
Multiple imputations (MAR) [4]	xxxx	xx.xx (xx.xx to xx.xx)	0.xxx	xxxx	xx.xx (xx.xx to xx.xx)	0.xxx
Multiple imputations (+1) [5]	xxxx	xx.xx (xx.xx to xx.xx)	0.xxx	xxxx	xx.xx (xx.xx to xx.xx)	0.xxx
Simple imputation (worst) [6]	xxxx	xx.xx (xx.xx to xx.xx)	0.xxx	xxxx	xx.xx (xx.xx to xx.xx)	0.xxx
Secondary outcomes						
NIHSS at Day 7 (ordinal)	xxxx	xx.xx (xx.xx to xx.xx)	0.xxx	xxxx	xx.xx (xx.xx to xx.xx)	0.xxx
NIHSS at Day 7 (continuous)	xxxx	xx.xx (xx.xx to xx.xx)	0.xxx	xxxx	xx.xx (xx.xx to xx.xx)	0.xxx
Poor outcome [mRS 3-6] at Day 90 (binary)	xxxx	xx.xx (xx.xx to xx.xx)	0.xxx	xxxx	xx.xx (xx.xx to xx.xx)	0.xxx
Death at Day 90 [mRS 6] (binary)	xxxx	xx.xx (xx.xx to xx.xx)	0.xxx	xxxx	xx.xx (xx.xx to xx.xx)	0.xxx
Dependency at Day 90 [mRS 3-5] (binary)	xxxx	xx.xx (xx.xx to xx.xx)	0.xxx	xxxx	xx.xx (xx.xx to xx.xx)	0.xxx
EQ-5D mobility (ordinal)	xxxx	xx.xx (xx.xx to xx.xx)	0.xxx			
EQ-5D self-care (ordinal)	xxxx	xx.xx (xx.xx to xx.xx)	0.xxx			
EQ-5D usual activities (ordinal)	xxxx	xx.xx (xx.xx to xx.xx)	0.xxx			
EQ-5D pain/discomfort (ordinal)	xxxx	xx.xx (xx.xx to xx.xx)	0.xxx			
EQ-5D anxiety/depression (ordinal)	xxxx	xx.xx (xx.xx to xx.xx)	0.xxx			
EQ-5D visual analog scale (continuous)	xxxx	xx.xx (xx.xx to xx.xx)	0.xxx			
Time to hospital discharge (survival)	xxxx	xx.xx (xx.xx to xx.xx)	0.xxx			
Place of residence at Day 90 (ordinal)	xxxx	xx.xx (xx.xx to xx.xx)	0.xxx			

(2) For ordinal, continuous and binary outcomes, the unadjusted model consists in a generalised linear mixed model with the appropriate distribution and link function. For survival outcomes, we use a Cox model. Unadjusted models include a random effect of site and the following fixed effects: randomised group, time from onset to recanalisation and NIHSS at admission.

(3) Adjusted models include the following additional baseline covariates: country of recruitment (if multiple countries), mRS before stroke (categorical), age (continuous) and sex (male vs female)

Programming notes:

- *add/edit footnotes as appropriate*
- *for the analysis of dependency alone, restrict denominator to subjects who are alive at 6 months (mRS 0-5)*
- *repeat this table in the per-protocol population*

Table 14. ICH outcomes

Raw counts and percentages								
Outcome / analysis method	Intensive BP lowering group	Guideline-recommended BP lowering group	Unadjusted model [1]			Adjusted model [2]		
			OR	(95% CI)	P-value	OR	(95% CI)	P-value
sICH by Heidelberg criteria	xxx/xxx xx.x%	xxx/xxx xx.x%	xx.xx	(xx.xx to xx.xx)	0.xxx	xx.xx	(xx.xx to xx.xx)	0.xxx
sICH by NIHSS criteria	xxx/xxx xx.x%	xxx/xxx xx.x%	xx.xx	(xx.xx to xx.xx)	0.xxx	xx.xx	(xx.xx to xx.xx)	0.xxx
sICH by SITS-MOST criteria	xxx/xxx xx.x%	xxx/xxx xx.x%	xx.xx	(xx.xx to xx.xx)	0.xxx	xx.xx	(xx.xx to xx.xx)	0.xxx
Any sICH within 90 days	xxx/xxx xx.x%	xxx/xxx xx.x%	xx.xx	(xx.xx to xx.xx)	0.xxx	xx.xx	(xx.xx to xx.xx)	0.xxx
Any ICH within 7 days	xxx/xxx xx.x%	xxx/xxx xx.x%	xx.xx	(xx.xx to xx.xx)	0.xxx	xx.xx	(xx.xx to xx.xx)	0.xxx

Programming notes:
- *repeat this table in the per-protocol population*

Table 15. SAEs

Event	Intensive BP lowering (N =)	Standard BP lowering (N =)	P-value
Any SAE	**nEVT nPT(xx.x%)**	**nEVT nPT(xx.x%)**	**0.xx**
Resulted in death	nEVT nPT(xx.x%)	nEVT nPT(xx.x%)	
Life threatening	nEVT nPT(xx.x%)	nEVT nPT(xx.x%)	
Requires prolonged hospitalisation	nEVT nPT(xx.x%)	nEVT nPT(xx.x%)	
Results in persistent or severe disability/incapacity	nEVT nPT(xx.x%)	nEVT nPT(xx.x%)	
Results in congenital anomaly/birth defect	nEVT nPT(xx.x%)	nEVT nPT(xx.x%)	
Medically significant	nEVT nPT(xx.x%)	nEVT nPT(xx.x%)	
MedDRA body system 1			
MedDRA preferred term a	nEVT nPT(xx.x%)	nEVT nPT(xx.x%)	
MedDRA preferred term b	nEVT nPT(xx.x%)	nEVT nPT(xx.x%)	
MedDRA preferred term c	nEVT nPT(xx.x%)	nEVT nPT(xx.x%)	
Etc. by descending frequency of body system and descending frequency of preferred term			

Programming note:
AEs will be summarised as the number (nPT) and proportion of patients experiencing at least one event. In addition, the total number of events (nEVT) will be reported. P-value from logistic regression. Repeat in per-protocol population.

Table 16. Causes of death

Cause	Intensive BP lowering (N =)	Standard BP lowering (N =)
Proximate cause of death	N=XXX	N=XXX
Most common cause #1	nnn xx%	nnn xx%
Most common cause #2	nnn xx%	nnn xx%
Etc.		
Most common cause #10	nnn xx%	nnn xx%
All other causes	nnn xx%	nnn xx%
Underlying causes of death	N=XXX	N=XXX
Most common cause #1	nnn xx%	nnn xx%
Most common cause #2	nnn xx%	nnn xx%
Etc.		
Most common cause #10	nnn xx%	nnn xx%
All other causes	nnn xx%	nnn xx%

Programming notes:

- *Order causes of death by descending frequency.*
- *Do not list categories with 0 deaths.*
- *Use number who died*
- *Depending on the distribution of deaths, we may choose to only report the x (e.g. 10) most common in the publication; however, the original table should include all causes with at least one patient.*
- *Repeat in per-protocol population*

Table 17. Protocol violations and deviations

Cause	Intensive BP lowering (N =)	Standard BP lowering (N =)
Eligibility violations	N=XXX	N=XXX
Age <18 years	nnn xx%	nnn xx%
Performed EVT ≥24 hours	nnn xx%	nnn xx%
Failed recanalisation (TICI <2b)	nnn xx%	nnn xx%
Not sustained SBP ≥140 mmHg within 3h after recanalisation		
Non-compliance with intervention	N=XXX	N=XXX
Reason 1	nnn xx%	nnn xx%
Reason 2	nnn xx%	nnn xx%
Etc.	nnn xx%	nnn xx%
Primary outcome	N=XXX	N=XXX
Non-blinded outcome assessment	nnn xx%	nnn xx%
Refused in-person or telephone assessment	nnn xx%	nnn xx%
Lost to follow-up	nnn xx%	nnn xx%
Etc.	nnn xx%	nnn xx%

Programming notes:

- *Reasons for non-compliance and missing outcome will be defined while blinded.*

Table 18. Form of assessment of 90 day outcomes

Cause	Intensive BP lowering (N =)	Standard BP lowering (N =)
Phone to patient	nnn xx%	nnn xx%
Face-to-face with patient	nnn xx%	nnn xx%
Phone to caregiver	nnn xx%	nnn xx%
Phone to patient's doctor or medical practitioner	nnn xx%	nnn xx%
Non-compliance with intervention	nnn xx%	nnn xx%
Other source of information	nnn xx%	nnn xx%

4.2 Figures

Figure 1: Consort flowchart

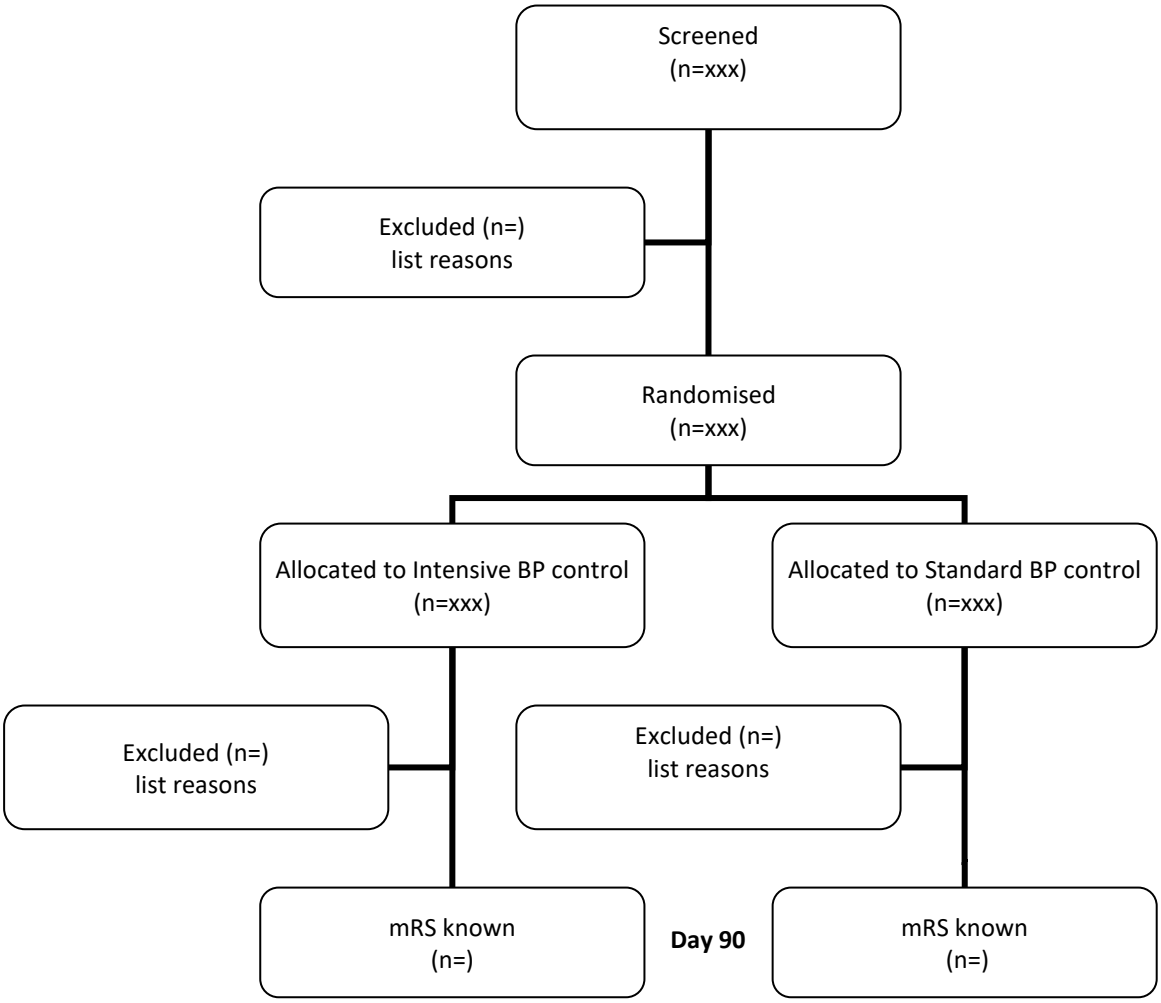

Figure 2. Blood pressure over time

Programming note: Longitudinal mean plot with 95% confidence intervals. Display denominators (N) under the x-axis at key timepoints. Show both SBP and DBP on a single plot. Display overall mean difference with 95% CI and p-value obtained from repeated-measure linear mixed models.

Figure 3. Grotta bar charts of mRS

Programming note: Stacked bar chart with 2 bars (intervention vs control) per visit. Each bar to be of the same high (100%). Show the proportion in each category using labels on the bars.

Figure 4: Boxplot of infarct and oedema size by follow-up assessment

Figure 5: Boxplot of NIHSS by follow-up assessment

Figure 6. Forest plot for subgroup analysis of mRS at 90 days

Figure 7. Cumulative incidence function of time to hospital discharge

Programming note: add number at risk every 10 days, median, quartiles, hazard ratio, 95% CI and P value from the Cox model.

4.3 Listings

Listing 1. Protocol deviations

Site ID	Patient ID	Date	Type of deviation	Description	Corrective action taken

Listing 2. Serious adverse events

Site ID	Patient ID	Date	Event description	Event code	Relationship with treatment	Outcome

Appendix 3: Proposed content and timing of primary and subsequent publications

N	2022
1	Main results paper: treatment effects of BP management on primary and secondary efficacy and safety outcomes, and according to pre-specified subgroups
	2023
2	Further subgroup analysis: relation of treatment effects by time, age, and neurological severity
3	Further subgroup analysis: treatment effects by baseline infarct size, collateral status, location of occluded vessel, use of antithrombotic therapy
4	Treatment effects on ICH, and infarct size and infarct growth
5	Individual patient data meta-analysis with other clinical trials of intensive BP lowering after EVT
6	Treatment effects on cerebral oedema
7	Association of BP parameters and outcomes
	2024 and subsequent years
8	Treatment effects according to utility-weighted mRS scores
9	Sex difference on stroke care in patients with EVT
10	Feasibility and cost-effectiveness of BP lowering for EVT treated AIS patients
11	Clinical and imaging predictors of poor outcome
12	Patterns and predictors of adverse outcomes (death, recurrent ischaemic stroke, ICH, coronary events) after EVT
13	Determinants of HRQoL and influence of age, sex, ethnicity, and level of disability
14	Regional variation in the management of EVT
15	Clinical-radiological correlations of baseline imaging and clinical and pathological classifications