**INTensive care bundle with blood pressure Reduction in Acute Cerebral
haemorrhage Trial: a stepped-wedge cluster clinical trial**

Statistical Analysis Plan

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1 Administrative information

1.1 Study identifiers

- Protocol Number: Version: 3.0, Date: 12 August 2019
- ClinicalTrials.gov register Identifier: [NCT03209258](#)
- Chinese Clinical Trial Registry: [ChiCTR-IOC-17011787](#)

1.2 Revision history

Version	Date	Details
0.1 (draft)	9 September 2021	First (internal) draft by Laurent Billot (LB), not circulated
0.2 (draft)	18 November 2021	First full draft. Sent to C Anderson and L Song for review. Did not include table shells.
0.3 (draft)	15 December 2021	Table shells added
0.4 (draft)	11 January 2022	Integrated further comments from Craig and Lili.
1.0 (final)	12 January 2022	Clarified the analysis of death and dependency. Sent to all authors for approval and sign-off.

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, Faculty of Medicine, 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
Prof Craig Anderson	The George Institute for Global Health, Faculty of Medicine, UNSW Sydney	Principal Investigator	Reviewed all versions
Prof Chao You	Department of Neurosurgery, West China Hospital, Sichuan University, Chengdu, China	Principal Investigator	Reviewed final version
Dr Xin Hu	Department of Neurosurgery, West China Hospital, Sichuan University, Chengdu, China	Project office	Reviewed final version
Dr Lu Ma	Department of Neurosurgery, West China Hospital, Sichuan University, Chengdu, China	Project office	Reviewed final version

Name and ORCID	Affiliation	Role on study	SAP contribution
Dr Menglu Ouyang	The George Institute for Global Health, Faculty of Medicine, UNSW Sydney	Research Associate	Reviewed all versions
Dr Xiaoying Chen	The George Institute for Global Health, Faculty of Medicine, UNSW Sydney	Project Manager	Reviewed all versions

1.3.2 Approvals

The undersigned have reviewed this plan and approve it as final. They find it to be consistent with the requirements of the protocol as it applies to their respective areas. They also find it to be compliant with International Conference on Harmonisation (ICH-E9) principles and in particular, confirm that this analysis plan was developed in a completely blinded manner (i.e. without knowledge of the effect of the intervention[s] being assessed).

Signature

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24/01/2022

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2 Introduction

2.1 Study synopsis

The INTensive care bundle with blood pressure Reduction in Acute Cerebral Haemorrhage trial (INTERACT3) is an international, multicentre, stepped-wedge (4 phases/3 steps), cluster randomised trial undertaken to assess a multifaceted intervention (i.e. Care Bundle) in a broad range of patients with acute spontaneous 'non-traumatic' intracerebral haemorrhage (ICH). The key objective is to determine the effectiveness of a goal-directed Care Bundle of time-critical protocols of active management that involve early physiological control (intensive blood pressure [BP] lowering, glycaemic control, and early treatment of pyrexia) and the reversal of anticoagulation therapy, compared with usual standard of care, on functional outcome in patients with ICH. The full protocol has been published in 2021.^[1]

Patient enrolment commenced in December 2017 and completed in December 2021. As of 31 December 2021, there have been over 7000 patients enrolled at a total of 122 activated sites in Brazil, China, Chile, India, Mexico, Nigeria, Pakistan, Peru, Sri Lanka and Vietnam. The activation of sites has finished. Patient follow-up will therefore be completed by June 2022, and the study closed out by November 2022. The main results are planned to be published in early 2023.

2.2 Study population

2.2.1 Site eligibility criteria

Hospital sites were eligible if they did not have established formal organisational protocols for the management of ICH, or if they used protocols different to those proposed in the study and approved a switch to the proposed interventional bundle as part of an intervention standard of care.

2.2.2 Patient eligibility criteria

- **Inclusion**

- Age ≥ 18 years
- Acute stroke syndrome presumed to be due to spontaneous ICH, defined as the sudden occurrence of bleeding into the parenchyma of the brain that may extend into the ventricles and, in rare cases, into the subarachnoid space, confirmed by clinical history and CT brain imaging. (NB Patients with ICH secondary to medical treatment [e.g. antiplatelet or antithrombotic therapy], are eligible, but ICH secondary to thrombolysis are ineligible)
- Presentation to hospital within 6 hours of stroke onset. (NB If the precise timing of the first symptoms or signs of the qualifying event are unknown then the time of onset will be taken as the last time at which the patient was known to be well)

- **Exclusions**

- Definite evidence that the ICH is secondary to a structural abnormality in the brain (e.g. an arteriovenous malformation [AVM], intracranial aneurysm, tumour, trauma, or previous cerebral infarction) or previous thrombolysis/thrombectomy
- A high likelihood that the patient will not adhere to the study treatment and follow-up regimen

In each case, the decision about the patient's eligibility was based on the attending clinician investigator's interpretation of the above eligibility criteria.

2.3 Interventions

2.3.1 Intervention arm

As soon as a site was activated, the project team used a range of implementation methods to introduce a goal-directed care bundle for application to consecutive eligible patients as a policy of usual care that involved the rapid correction (<1 hour) of physiological variables as soon as the abnormalities were recognised, and for the target to be maintained in patients for 7 days or hospital discharge (or death, if sooner). These interventions were:

1. intensive BP lowering to a systolic target of <140mmHg;
2. glucose control to a target of 6.1-7.8 mmol/L and 7.8-10.0 mmol/L for patients without and with diabetes, respectively;
3. treatment of pyrexia by any means to a target body temperature $\leq 37.5^{\circ}\text{C}$;
4. reversal of anticoagulation to target INR <1.5 involving the use of vitamin K and prothrombin complex concentrate (PCC) or alternatively, fresh frozen plasma (FFP).

2.3.2 Usual Care arm

As soon as a site was activated, patients in the Usual Care group received standard of care. The decisions about the location of such care delivery, investigations, monitoring, and all treatments, was at the discretion of the treating clinical team.

2.3.3 Background standard of care

Data collected in all patients included their management, including the insertion of invasive monitoring devices, intravenous fluid resuscitation, BP lowering, vasoactive support, glycaemic control, mechanical ventilation, neurosurgery, and other supportive therapy.

2.4 Outcomes

The study outcomes are:

2.4.1 Primary outcome

- The primary outcome is according to scores on the modified Rankin scale (mRS) at 6 months, analysed as an ordinal outcome (categories 0 to 6).

2.4.2 Secondary outcomes

- Death or dependency according to severity of neurological impairment on the National Institute of Health Stroke Scale (NIHSS) at 7 days
- The following at 6 months:
 - Poor outcome, defined by mRS scores of 3-6;
 - Death;
 - Disability (mRS scores 3-5);
 - Health-related quality of life (HRQoL) using the EuroQoL Group 5-Dimension self-report questionnaire (EQ-5D);
 - Duration of hospitalisation;
 - Residence.

2.4.3 Safety outcomes

- Serious adverse events (SAEs) during follow-up

2.5 Randomisation and blinding

The unit of randomisation was the hospital site, randomly assigned by a statistician not otherwise involved in the study to 3 groups using a pre-specified randomisation schedule with permuted blocks. Participating sites were stratified according to country and estimated recruitment capacity (i.e. size) of the site.

2.6 Statistical hypotheses

The primary statistical hypotheses are as follows:

- **Null hypothesis:** no difference in mRS scores at 6 months between those randomised to Care Bundle and Usual Care, that is odds ratio (OR) (Care Bundle vs Usual Care) = 1
- **Alternative hypothesis (2-sided):** OR (Intervention vs Usual Care) $\neq$ 1, with the expectation participants randomised to the Care Bundle would have a lower/better mRS score (OR<1).

2.7 Sample size

The study is designed with 90% power ($p=0.05$) to detect a 20% reduction in the odds (common OR of 0.80) of a worse outcome using an ordinal logistic regression. Assuming a distribution of mRS in the usual care arm that is similar to the one observed in the standard BP arm of the second phase of Intensive Blood Pressure Reduction in Acute Cerebral Haemorrhage Trial (INTERACT2),^[2] that is 7.6%, 18.0%, 18.8%, 16.6%, 19.0%, 8.0% and 12.0% for mRS scores of 0 to 6, respectively, which corresponds to a 5.6% absolute improvement in the proportion of patients experiencing a bad outcome (mRS of 3-6), from 55.6% down to 50%. This also translates to a modest 10% relative risk reduction (relative risk of 0.90).

The study planned to recruit 110 sites in a stepped-wedge design, consisting of 3 groups and 4 phases. Each group would, therefore, include approximately 36 sites. Assuming an intraclass correlation coefficient (ICC) of 0.044, which is similar to that found in the INTERACT2^[2] and the Head Position in Acute Stroke Trial (HeadPoST),^[3] which included large numbers of hospitals in China, each site would be required to recruit an average of 18 patients per phase. Accounting for 5% of participants with a missing outcome, each site would need to target an average of 19 patients per phase, thus leading to a total sample size of 8,360 patients (110 sites $\times$ 4 phases $\times$ 19 patients).

3 Statistical analysis

3.1 Statistical principles

3.1.1 Level of statistical significance

Two formal interim analysis were planned and undertaken using the Haybittle-Peto stopping rule (3 standard-deviations) for efficacy.^[4] Given the conservative rule used and the negligible amount of type-I error rate spent at the two interim analyses, the significance threshold will remain at 5% for the final analysis.

Final analyses of the primary outcome, including sensitivity analyses, will all be conducted using a two-sided significance level of 5%.

For the seven secondary clinical outcomes, we will control the family-wise error rate by applying a sequential Holm-Sidak correction.^[5] 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 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 or the models with varying time trends). For HRQoL, it will only apply to the analysis of the overall score.

No multiplicity correction will be applied to other statistical tests.

3.1.2 Statistical software

Analyses will be conducted primarily using SAS software (version 9.3 or above).

3.2 Analysis populations

Due to the stepped-wedge design, the group allocation for a patient is determined by the site and by the period during which they participated, regardless of treatment adherence.

The intention-to-treat analysis set will be used to assess both effectiveness and safety. The flow of patients through the study will be displayed in a CONSORT diagram (Figure 1). Details will be obtained as to the type of assessment performed (phone, face-to-face, etc.) and analyses will be undertaken according to recent reporting guidelines for stepped-wedge cluster randomised trials.^[6]

Per-protocol analyses and other analyses adjusting for compliance are planned as part of secondary publications.

3.3 Impact of COVID

The COVID pandemic, which emerged during conduct of the trial in China and activation of sites elsewhere in the world, had a significant impact on recruitment in multiple countries. Thus, several analyses will be undertaken to assess the potential impact of COVID on the INTERACT3 intervention. These analyses will include baseline and time adjustments as well as subgroup analysis. We have defined two periods in relation to COVID: 'before' (30 January 2020) vs 'during/after' (from 1 February 2020) the pandemic. Deaths due to COVID will also be reported.

3.4 Changes from the protocol

In the published protocol,^[1] it was stated that models will be adjusted for site size which was a stratification variable. Given that size was defined differently in China compared to other countries, and that some strata contain small numbers of sites, we have subsequently decided not to include size site as a covariate.

Although we indicated that no adjustment for multiplicity would be performed, we now feel that adjusting the family-wise error rate across the seven secondary outcomes would be more appropriate.

Both these changes are made in a blinded manner and independent of any trial result.

3.5 Baseline analyses

3.5.1 Cluster characteristics

Description of the cluster characteristics (e.g. location, size) will be presented by treatment group. Discrete variables will be summarised by frequencies and percentages. Percentages will be calculated according to the number of clusters with available data. Continuous variables will be summarised by using mean and standard deviation (SD), and median and interquartile range (Q1-Q3).

3.5.2 Patient characteristics

Description of the baseline characteristics will be presented by treatment group and by study period. Discrete variables will be summarised by frequencies and percentages. Percentages will be calculated according to the number of patients in whom data are available. Continuous variables will be summarised by using mean and SD, and median and interquartile range (Q1-Q3). No adjustment for clustering will be applied when summarising baseline characteristics. To assess whether the profile of patients enrolled changed over time due to COVID, we will also describe baseline characteristics according to COVID period (see Section 3.3).

Baseline measures will include all socio-demographic, clinical and medical information collected at baseline.

3.6 Assessments and interventions conducted between Day 1 and Day 7

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.

3.7 Laboratory values and vital signs

Laboratory values and vital signs collected repeatedly over the first 24 hours and 7 days will be described using longitudinal mean plots and analysed using repeated-measure linear mixed models. This will apply to systolic BP, diastolic BP, blood glucose, and body temperature. The intervention effect will be estimated using a similar approach as the primary analysis model described in Section 3.8.1, but with the following differences:

- (a) given the continuous nature of the outcome, a normal distribution and identity link will be used;
- (b) the model will include all available post-baseline measurements per subject with within-subject correlations modelled using a repeated effect with a compound-symmetry covariance structure, and;
- (c) the baseline value of the outcome will be added as a fixed covariate.

The effect of the intervention at 1 hour and 24 hours will be estimated from the model as the adjusted mean difference and 95% CI.

The proportion of patients reaching each treatment target (e.g. systolic BP <140 mmHg) will be reported by treatment group. For these analyses, the denominators will consist in patients who were eligible for the corresponding target. For example, only patients with a systolic BP ≥ 140 mmHg at baseline will be included in the analysis of systolic BP target. For those reaching target, we will also describe the time take to reach the corresponding target. No formal statistical tests will be performed on these metrics.

These analyses are only applicable to the subset of subjects meeting the relevant eligibility criteria at baseline (e.g. glucose control was only applicable to subjects outside of the recommended glucose targets at baseline) and will include all data available.

3.8 Analysis of the primary outcome

The primary outcome of the mRS at 6 months 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 usual care arm obtained from an ordinal logistic model (defined below).

3.8.1 Main analysis

The primary analysis will be conducted by extending the approach developed by Hussey and Hughes for the analysis of stepped-wedge trials^[7] to an ordinal outcome. We will be using an ordinal logistic regression with a random effect for cluster (hospital site), a fixed effect indicating the group assignment of each cluster at each step, and a fixed categorical effect of time (each step). The corresponding cumulative logit model can be written as follows:

$$\text{logit}(P\{Y_{ijk} \leq m\}) = \mu_m + \theta X_{ij} + \beta_j + c_i + e_{ijk} \quad (\text{model 1})$$

where:

Y_{ijk} denotes the outcome of subject k in period j within cluster i

μ_m is the intercept corresponding to a mRS score of m ($m=0, 1, 2, 3, 4, 5, 6$)

X_{ij} is a binary variable indicating group allocation during period j for cluster i with $X_{ij} = 1$ for intervention and $X_{ij} = 0$ for control

θ is the parameter of interest estimating the fixed effect of the intervention and where $\exp(\theta)$ is the OR

β_j is a fixed categorical period effect

c_i is a random cluster effect with $c_i \sim N(0, \sigma_c^2)$

e_{ijk} are individual-level errors following a multinomial distribution

The effect of the intervention will be presented as the OR of a worse outcome and its 95% confidence interval (CI) using the usual care 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 usual care arm).

Randomisation was stratified by country and size of site, defined as the expected number of recruited patients. Given the large number of strata, and that the primary analysis is already adjusted by site, the main analysis model will not further adjust for country or size of site. Further adjustments will, however, be performed as sensitivity analyses (see Section 3.8.3).

We will test the proportional-odds assumption in Model 1. In case of violation, we will proceed with the analysis and interpret the intervention odds ratio as an average effect across all mRS levels 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 3.9.2).

3.8.2 Allowing time trends to vary by cluster

The base model developed by Hussey and Hughes makes the implicit assumption that the effect of time is common across all clusters. Given the large number of clusters and that sites entered the study at different times, an additional model will be run to allow the effect of time to vary randomly across sites, as described by Hemming et al.^[8] This will be done by adding v_{ij} , a random interaction between period and cluster with $v_{ij} \sim N(0, \sigma_v^2)$ to Model 1, which becomes:

$$\text{logit}(P\{Y_{ijk} \leq m\}) = \mu_m + \theta X_{ij} + \beta_j + c_i + v_{ij} + e_{ijk} \quad (\text{model 2})$$

The addition of a random period-by-cluster interaction will allow the intracluster correlation to vary depending on whether subjects from the same cluster are from the same period or from a different period. This model will also include adjustment by country and size of site.

3.8.3 Adjusted analyses

The two models described in Sections 3.8.1 and 3.8.2 will be re-run after adding the following individual baseline covariates as fixed effects:

- Country (grouped as China vs. India/Pakistan/Sri Lanka/Vietnam vs. Brazil/Peru/Chile/Mexico/Nigeria)
- mRS before stroke (categorical variable)
- Age (continuous)
- Sex (male vs female)
- Baseline NIHSS score (continuous)

Should the examination of baseline characteristics by COVID period reveal important changes in patient characteristics over time (see Section 3.5.2), additional baseline variables will be added as covariates. This decision will be made whilst blind to the intervention effect and, if implemented, would lead to two additional adjusted models (i.e. adding to the previous two models which include country, mRS, age, sex and NIHSS score).

3.8.4 Subgroup analyses

The following subgroup analyses are planned for the primary outcome, regardless of the statistical significance for the primary analysis:

- Age: <60, 60-<70, 70-<80, 80+
- Sex: male vs. female
- Country: China vs. India/Pakistan/Sri Lanka/Vietnam vs. Brazil/Peru/Chile/Mexico/Nigeria
- NIHSS: <15 vs. ≥15
- Baseline haematoma volume: <15 ml vs. 15-<30ml vs. ≥30ml
- Baseline haematoma location: cortical vs. deep vs. brainstem/cerebellar/primary ventricular. In case of multiple locations, the following hierarchy will be used to allocate a 'primary' location: 1) Deep, 2) Cortical, 3) Other.

Each subgroup analysis will be performed by adding the subgroup variable as well as its interaction with the intervention as fixed effects to the logistic regression model used for the primary analysis (see Section 3.8.1). Within each subgroup, summary measures will include raw counts and percentages within each treatment arm, as well as the OR for treatment effect with 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 the subgroup variable.

Other subgroup analyses for exploratory purposes include:

- Country: by individual countries and grouped by economic development (low-middle vs. high-middle [including high income country, Chile])
- Site: by size (small [<500 beds] vs. medium [500-999] beds vs. large [1000+] beds) and type (tertiary vs. secondary)
- Time from onset: by hour

3.8.5 Treatment of missing data

The proportion of data missing for the primary outcome (mRS at 6 months) will be described overall, by study period and by COVID period (see Section 3.3), while blinded to the intervention. Reasons for missing data will be described overall and by intervention arm. In case of non-negligible amounts of missing data (>10%) or changes in missing data patterns overtime, 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.^[9]

We will first run an imputation model under the missing at random (MAR) assumption. This MAR imputation model will use fully conditional specification (FCS)^[10] and will include the following variables: mRS at 6 months, the NIHSS and mRS scores at 7 days (or hospital discharge, if sooner), a variable indicating the cluster (hospital), a variable indicating the stepped-wedge period, a variable indicating the intervention, and all key socio-demographic, clinical, and medical baseline variables. The mRS at 6 months 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 3.8.1. 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 6 months 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). 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 6 months with a score of 6, thus assuming all subjects with missing data have died. While this assumption is unlikely to hold in most cases, it is plausible that some subjects may have become uncontactable due to death after hospital discharge.

3.9 Analysis of secondary outcomes

3.9.1 NIHSS score at 7 days

The NIHSS score at 7 days will be categorized 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 3.8.1. As a sensitivity analysis, the NIHSS score will also be analysed as a continuous variable using an unadjusted hierarchical linear regression model 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. We will also apply the model

with varying time trends (Section 3.8.2) as well as the covariate adjustments described in Section 3.8.3; however, no subgroup or imputed analysis will be performed on this outcome.

3.9.2 Binary analysis of mRS at 6 months

A binary analysis of the mRS at 6 months will be performed by dichotomizing the mRS as either 'poor' (scores 3-6) or 'favourable' (scores 0-2) outcomes. This analysis will be conducted using an unadjusted hierarchical logistic regression similar to Model 1 (see Section 3.8.1), 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 model with varying time trends (Section 3.8.2) as well as the covariate adjustments described in Section 3.8.3; however, no subgroup or imputed analysis will be performed on this outcome. A similar analysis will be performed on mortality alone (mRS of 6) and on dependency alone (mRS 3-5). For dependency alone, the analysis will be restricted to subjects who are alive at 6 months (mRS 0-5).

3.9.3 HRQoL

Each of the five EQ-5D dimensions will be analysed via ordinal logistic regression using the same model as for the primary analysis of mRS at 6 months (Section 3.8.1). 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 only plan to apply the primary model to these HRQoL outcomes (i.e. neither the model with varying time trends, nor the adjusted or subgroup analyses). Further analyses of EQ-5D will be undertaken as part of the economic evaluations, which is outside the scope of this SAP.

3.9.4 Duration of hospitalisation

Duration of hospitalisation will be analysed as time to discharge censored at 6 months or when the subject was last known to be alive and in hospital, whichever is earlier. It will be summarized 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.^[11] Similar to the primary analysis model (Section 3.8.1), the Cox model will include a fixed categorical period effect as well as a binary variable indicating the group allocation during each period in each cluster. To model potential within-cluster correlations, we will use a shared-parameter frailty Cox model with a random site effect.^[12] We only plan to apply the primary model to this outcome (i.e. neither the model with varying time trends, nor the adjusted or subgroup analyses).

3.9.5 Residence

The patient's place of residence at 6 months will be described using all possible categories then analysed as a binary outcome using the same approach as for the binary analysis of the mRS at 6 months (Section 3.9.2). 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

We only plan to apply the primary model to this outcome (i.e. neither the model with varying time trends, nor the adjusted or subgroup analyses).

3.9.6 SAEs

SAEs will be summarised as the number of events as well as the number and proportion of patients experiencing at least one 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 3.9.2). Primary and underlying causes of deaths will be summarised by treatment arm with no formal test.

4 References

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5 Proposed outputs

5.1 Tables

Table 1. Number of subjects enrolled and with primary outcome data per group and per period

Group	Period 1	Period 2	Period 3	Period 4	Total
1 (xx sites)	xxx / xxx (xx%)	xxx / xxx (xx%)	xxx / xxx (xx%)	xxx / xxx (xx%)	xxx / xxx (xx%)
2 (xx sites)	xxx / xxx (xx%)	xxx / xxx (xx%)	xxx / xxx (xx%)	xxx / xxx (xx%)	xxx / xxx (xx%)
3 (xx sites)	xxx / xxx (xx%)	xxx / xxx (xx%)	xxx / xxx (xx%)	xxx / xxx (xx%)	xxx / xxx (xx%)
Total (xxx sites)	xxx / xxx (xx%)	xxx / xxx (xx%)	xxx / xxx (xx%)	xxx / xxx (xx%)	xxx / xxx (xx%)

Notes: the denominator represents the number of subjects enrolled during the period. The numerator represents the number of subjects with a primary endpoint measure (mRS at 6 months). Cells shaded in grey represent usual care periods. Cells shaded in orange represent care bundle periods.

Table 2. Baseline characteristics

	Care Bundle (N =)	Usual Care (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
Han Chinese	xxx xx.x%	xxx xx.x%	xxx xx.x%
Non-Han Chinese	xxx xx.x%	xxx xx.x%	xxx xx.x%
Caucasian/European	xxx xx.x%	xxx xx.x%	xxx xx.x%
Latin American	xxx xx.x%	xxx xx.x%	xxx xx.x%
Mixed	xxx xx.x%	xxx xx.x%	xxx xx.x%
Other Asian	xxx xx.x%	xxx xx.x%	xxx xx.x%
Indian Subcontinent	xxx xx.x%	xxx xx.x%	xxx xx.x%
Other	xxx xx.x%	xxx xx.x%	xxx xx.x%
Place of residency	xxx	xxx	xxx
Own home	xxx xx.x%	xxx xx.x%	xxx xx.x%
Family member's home	xxx xx.x%	xxx xx.x%	xxx xx.x%
Care facility (eg nursing home, hostel, shelter, community based care)	xxx xx.x%	xxx xx.x%	xxx xx.x%
Other	xxx xx.x%	xxx xx.x%	xxx xx.x%
Main occupation pre-stroke	xxx	xxx	xxx
Professional, executive	xxx xx.x%	xxx xx.x%	xxx xx.x%
Business	xxx xx.x%	xxx xx.x%	xxx xx.x%
Sales and service	xxx xx.x%	xxx xx.x%	xxx xx.x%
Driver	xxx xx.x%	xxx xx.x%	xxx xx.x%
Farmer, labourer	xxx xx.x%	xxx xx.x%	xxx xx.x%
Home duties	xxx xx.x%	xxx xx.x%	xxx xx.x%
Other	xxx xx.x%	xxx xx.x%	xxx xx.x%
Highest education degree completed	xxx	xxx	xxx
Primary school	xxx xx.x%	xxx xx.x%	xxx xx.x%

	Care Bundle (N =)	Usual Care (N =)	Total (N =)
Junior school	xxx xx.x%	xxx xx.x%	xxx xx.x%
High school	xxx xx.x%	xxx xx.x%	xxx xx.x%
Undergraduate (bachelor degree)	xxx xx.x%	xxx xx.x%	xxx xx.x%
Postgraduate (master degree or higher)	xxx xx.x%	xxx xx.x%	xxx xx.x%
Never had education	xxx xx.x%	xxx xx.x%	xxx xx.x%
Height (cm)	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
Weight (kg)	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
Body Mass Index	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
Systolic Blood Pressure (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
Diastolic Blood Pressure (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
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)

	Care Bundle (N =)	Usual Care (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
Body Temperature (°C)	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
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	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	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%

	Care Bundle (N =)	Usual Care (N =)	Total (N =)
5=Orientated	xxx xx.x%	xxx xx.x%	xxx xx.x%
Motor Response	xxx	xxx	xxx
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%
Used anticoagulation	xxx	xxx	xxx
Yes	xxx xx.x%	xxx xx.x%	xxx xx.x%
No	xxx xx.x%	xxx xx.x%	xxx xx.x%
INR 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
Haematoma present	xxx	xxx	xxx
Yes	xxx xx.x%	xxx xx.x%	xxx xx.x%
No	xxx xx.x%	xxx xx.x%	xxx xx.x%
Initial volume of haematoma (mL)	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
Side of haematoma	xxx	xxx	xxx
Left	xxx xx.x%	xxx xx.x%	xxx xx.x%
Right	xxx xx.x%	xxx xx.x%	xxx xx.x%
Midline	xxx xx.x%	xxx xx.x%	xxx xx.x%
Site of haematoma	xxx	xxx	xxx
Cortical	xxx xx.x%	xxx xx.x%	xxx xx.x%
Deep	xxx xx.x%	xxx xx.x%	xxx xx.x%
Cerebellum	xxx xx.x%	xxx xx.x%	xxx xx.x%
Brainstem	xxx xx.x%	xxx xx.x%	xxx xx.x%

	Care Bundle (N =)	Usual Care (N =)	Total (N =)
Intraventricular blood present	xxx	xxx	xxx
Yes	xxx xx.x%	xxx xx.x%	xxx xx.x%
No	xxx xx.x%	xxx xx.x%	xxx xx.x%
Volume of intraventricular blood (mL)	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
Admission service	xxx	xxx	xxx
Neurosurgery	xxx xx.x%	xxx xx.x%	xxx xx.x%
Neurology	xxx xx.x%	xxx xx.x%	xxx xx.x%
Intensive care	xxx xx.x%	xxx xx.x%	xxx xx.x%
Emergency department	xxx xx.x%	xxx xx.x%	xxx xx.x%
Other	xxx xx.x%	xxx xx.x%	xxx xx.x%
Clinician's opinion of patient surviving next 48 hours	xxx	xxx	xxx
Yes	xxx xx.x%	xxx xx.x%	xxx xx.x%
No	xxx xx.x%	xxx xx.x%	xxx xx.x%
Level of certainty of prognosis	xxx	xxx	xxx
Definite no	xxx xx.x%	xxx xx.x%	xxx xx.x%
Possible no	xxx xx.x%	xxx xx.x%	xxx xx.x%
Uncertain	xxx xx.x%	xxx xx.x%	xxx xx.x%
Possible yes	xxx xx.x%	xxx xx.x%	xxx xx.x%
Definite yes	xxx xx.x%	xxx xx.x%	xxx xx.x%
Years of practice of doctor giving prognosis	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
Final diagnosis			
Hypertension-related ICH	xxx xx.x%	xxx xx.x%	xxx xx.x%
Presumed amyloid angiopathy	xxx xx.x%	xxx xx.x%	xxx xx.x%
AVM	xxx xx.x%	xxx xx.x%	xxx xx.x%

	Care Bundle (N =)	Usual Care (N =)	Total (N =)
Aneurysm	xxx xx.x%	xxx xx.x%	xxx xx.x%
Other vascular abnormality	xxx xx.x%	xxx xx.x%	xxx xx.x%
Tumour	xxx xx.x%	xxx xx.x%	xxx xx.x%
Systemic/other disease	xxx xx.x%	xxx xx.x%	xxx xx.x%
Anticoagulation	xxx xx.x%	xxx xx.x%	xxx xx.x%
Other definite pathology	xxx xx.x%	xxx xx.x%	xxx xx.x%
Uncertain aetiology	xxx xx.x%	xxx xx.x%	xxx xx.x%

Table 3. Medical history

Variable	Care Bundle (N =)	Usual Care (N =)	Total (N =)
Intracerebral haemorrhage	xxx/xxx xx.x%	xxx/xxx xx.x%	xxx/xxx xx.x%
Ischaemic stroke	xxx/xxx xx.x%	xxx/xxx xx.x%	xxx/xxx xx.x%
Stroke of unknown type	xxx/xxx xx.x%	xxx/xxx xx.x%	xxx/xxx xx.x%
Acute coronary syndrome (STEMI/NSTEMI)	xxx/xxx xx.x%	xxx/xxx xx.x%	xxx/xxx xx.x%
Atrial fibrillation	xxx/xxx xx.x%	xxx/xxx xx.x%	xxx/xxx xx.x%
Heart failure	xxx/xxx xx.x%	xxx/xxx xx.x%	xxx/xxx xx.x%
Other heart disease	xxx/xxx xx.x%	xxx/xxx xx.x%	xxx/xxx xx.x%
Hypertension	xxx/xxx xx.x%	xxx/xxx xx.x%	xxx/xxx xx.x%
Hypertension on treatment	xxx/xxx xx.x%	xxx/xxx xx.x%	xxx/xxx xx.x%
Diabetes mellitus	xxx/xxx xx.x%	xxx/xxx xx.x%	xxx/xxx xx.x%
Hypercholesterolaemia	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%
Epilepsy	xxx/xxx xx.x%	xxx/xxx xx.x%	xxx/xxx xx.x%
Liver disease	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%
Current alcohol use	xxx/xxx xx.x%	xxx/xxx xx.x%	xxx/xxx xx.x%
Other major health condition(s) that limits daily activity	xxx/xxx xx.x%	xxx/xxx xx.x%	xxx/xxx xx.x%

Table 4. Medications at time of admission

Variable	Care Bundle (N =)	Usual Care (N =)	Total (N =)
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%
Heparin (unfractionated or low molecular weight)	xxx xx.x%	xxx xx.x%	xxx xx.x%
Other anticoagulant	xxx xx.x%	xxx xx.x%	xxx xx.x%
Type of new oral anticoagulant	xxxx	xxxx	xxxx
Dabigatran	xxx xx.x%	xxx xx.x%	xxx xx.x%
Rivaroxaban	xxx xx.x%	xxx xx.x%	xxx xx.x%
Apixaban	xxx xx.x%	xxx xx.x%	xxx xx.x%
Type of Heparin	xxxx	xxxx	xxxx
Subcutaneous low-dose for VTE prophylaxis	xxx xx.x%	xxx xx.x%	xxx xx.x%
Subcutaneous full-dose for treatment	xxx xx.x%	xxx xx.x%	xxx xx.x%
Intravenous therapy	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%
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%
Blood glucose lowering agents used	xxx/xxx xx.x%	xxx/xxx xx.x%	xxx/xxx xx.x%

Variable	Care Bundle (N =)	Usual Care (N =)	Total (N =)
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%
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%
Anti-epilepsy drugs used	xxx/xxx xx.x%	xxx/xxx xx.x%	xxx/xxx xx.x%
Type of anti-epilepsy drugs	xxxx	xxxx	xxxx
Sodium valproate	xxx xx.x%	xxx xx.x%	xxx xx.x%
Levetiracetam	xxx xx.x%	xxx xx.x%	xxx xx.x%
Carbamazepine	xxx xx.x%	xxx xx.x%	xxx xx.x%
Phenytoin	xxx xx.x%	xxx xx.x%	xxx xx.x%
Other anti-epilepsy agents	xxx xx.x%	xxx xx.x%	xxx xx.x%

Table 5. Laboratory and vital measures recorded during the first 24 hours

Variable	Care Bundle (N =)	Usual Care (N =)	Total (N =)
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
Highest blood glucose (mmol/L)	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 blood glucose (mmol/L)	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 body temperature (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 body temperature (mmHg)	xxx	xxx	xxx
Mean (SD)	xxx.x (xxx.x)	xxx.x (xxx.x)	xxx.x (xxx.x)

Variable	Care Bundle (N =)	Usual Care (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
INR at Day 1	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 6. Antihypertensive and hypothermia treatments administered during the first 24 hours

Variable	Care Bundle (N =)	Usual Care (N =)	Total (N =)
IV hypertensive 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%
Hypothermia treatment	xxx/xxx xx.x%	xxx/xxx xx.x%	xxx/xxx xx.x%
Type of hypothermia 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 7. Management care administered until Day 7

Variable	Care Bundle (N =)	Usual Care (N =)	Total (N =)
IV hypertensive treatment	xxx/xxx xx.x%	xxx/xxx xx.x%	xxx/xxx xx.x%
Oral hypertensive treatment	xxx/xxx xx.x%	xxx/xxx xx.x%	xxx/xxx xx.x%
Insulin	xxx/xxx xx.x%	xxx/xxx xx.x%	xxx/xxx xx.x%
Hypothermia treatment	xxx/xxx xx.x%	xxx/xxx xx.x%	xxx/xxx xx.x%
FFP	xxx/xxx xx.x%	xxx/xxx xx.x%	xxx/xxx xx.x%
Vitamin K	xxx/xxx xx.x%	xxx/xxx xx.x%	xxx/xxx xx.x%
PCC	xxx/xxx xx.x%	xxx/xxx xx.x%	xxx/xxx xx.x%
Mannitol	xxx/xxx xx.x%	xxx/xxx xx.x%	xxx/xxx xx.x%
Hyperosmolar saline	xxx/xxx xx.x%	xxx/xxx xx.x%	xxx/xxx xx.x%
Antibiotic treatment	xxx/xxx xx.x%	xxx/xxx xx.x%	xxx/xxx xx.x%
Anti-epilepsy drugs	xxx/xxx xx.x%	xxx/xxx xx.x%	xxx/xxx xx.x%
Dexamethasone	xxx/xxx xx.x%	xxx/xxx xx.x%	xxx/xxx xx.x%
Statins	xxx/xxx xx.x%	xxx/xxx xx.x%	xxx/xxx xx.x%
Any decompressive surgery	xxx/xxx xx.x%	xxx/xxx xx.x%	xxx/xxx xx.x%
Craniotomy	xxx/xxx xx.x%	xxx/xxx xx.x%	xxx/xxx xx.x%
Craniectomy	xxx/xxx xx.x%	xxx/xxx xx.x%	xxx/xxx xx.x%
Endoscopy	xxx/xxx xx.x%	xxx/xxx xx.x%	xxx/xxx xx.x%
Intraventricular drainage	xxx/xxx xx.x%	xxx/xxx xx.x%	xxx/xxx xx.x%
Catheterisation with/without thrombolysis	xxx/xxx xx.x%	xxx/xxx xx.x%	xxx/xxx xx.x%
Other surgery	xxx/xxx xx.x%	xxx/xxx xx.x%	xxx/xxx xx.x%
Endotracheal intubation	xxx/xxx xx.x%	xxx/xxx xx.x%	xxx/xxx xx.x%
Mechanical ventilation	xxx/xxx xx.x%	xxx/xxx xx.x%	xxx/xxx xx.x%
Airways suction of secretions	xxx/xxx xx.x%	xxx/xxx xx.x%	xxx/xxx xx.x%
Urinary catheter insertion	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%
Acute stroke unit admission	xxx/xxx xx.x%	xxx/xxx xx.x%	xxx/xxx xx.x%
Pneumatic calf compression	xxx/xxx xx.x%	xxx/xxx xx.x%	xxx/xxx xx.x%
Physiotherapy	xxx/xxx xx.x%	xxx/xxx xx.x%	xxx/xxx xx.x%
Occupational therapy	xxx/xxx xx.x%	xxx/xxx xx.x%	xxx/xxx xx.x%
Psychological therapy	xxx/xxx xx.x%	xxx/xxx xx.x%	xxx/xxx xx.x%
Intravenous traditional Chinese medicine	xxx/xxx xx.x%	xxx/xxx xx.x%	xxx/xxx xx.x%
Intravenous neuroprotective agent	xxx/xxx xx.x%	xxx/xxx xx.x%	xxx/xxx xx.x%
Clinical decision to withdraw active care	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%
Ward/Department where patient stayed longest			
Neurosurgery	xxx/xxx xx.x%	xxx/xxx xx.x%	xxx/xxx xx.x%
Neurology	xxx/xxx xx.x%	xxx/xxx xx.x%	xxx/xxx xx.x%

Variable	Care Bundle (N =)	Usual Care (N =)	Total (N =)
Intensive care	xxx/xxx xx.x%	xxx/xxx xx.x%	xxx/xxx xx.x%
Emergency department	xxx/xxx xx.x%	xxx/xxx xx.x%	xxx/xxx xx.x%
Other	xxx/xxx xx.x%	xxx/xxx xx.x%	xxx/xxx xx.x%
Prognosis, will patient survive next 6 months			
Definitely no	xxx/xxx xx.x%	xxx/xxx xx.x%	xxx/xxx xx.x%
Possible no	xxx/xxx xx.x%	xxx/xxx xx.x%	xxx/xxx xx.x%
Uncertain	xxx/xxx xx.x%	xxx/xxx xx.x%	xxx/xxx xx.x%
Possible yes	xxx/xxx xx.x%	xxx/xxx xx.x%	xxx/xxx xx.x%
Definite yes	xxx/xxx xx.x%	xxx/xxx xx.x%	xxx/xxx xx.x%

Table 8. Details of hypertensive treatments between Days 2 and 7

Variable	Care Bundle (N =)	Usual Care (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 9. Treatment targets

Variable	Care Bundle (N =)	Usual Care (N =)	Total (N =)
Baseline SBP ≥ 140 mmHg	xxx/xxx xx.x%	xxx/xxx xx.x%	xxx/xxx xx.x%
SBP target < 140 mmHg achieved	xxx/xxx xx.x%	xxx/xxx xx.x%	xxx/xxx xx.x%
Time to achieving SBP target (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
Baseline Glucose < 6.1 or > 7.8 mmol/L for non-diabetic (< 7.8 or > 10.0 mmol/L for diabetic patients)	xxx/xxx xx.x%	xxx/xxx xx.x%	xxx/xxx xx.x%
Blood glucose target achieved	xxx/xxx xx.x%	xxx/xxx xx.x%	xxx/xxx xx.x%
Time to achieving blood glucose target (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
Baseline Temperature (> 37.5 °C)	xxx/xxx xx.x%	xxx/xxx xx.x%	xxx/xxx xx.x%
Temperature target of achieved	xxx/xxx xx.x%	xxx/xxx xx.x%	xxx/xxx xx.x%
Time to achieving temperature target (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
Baseline INR ≥ 1.5	xxx/xxx xx.x%	xxx/xxx xx.x%	xxx/xxx xx.x%
INR target achieved	xxx/xxx xx.x%	xxx/xxx xx.x%	xxx/xxx xx.x%
Time to achieving INR target (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

Table 10. Clinical outcomes

Outcome / analysis method	Unadjusted model ¹				Adjusted model ²			
	N	OR/MD/HR (95% CI)	P	ICC	N	OR/MD/HR (95% CI)	P	ICC
mRS at Month 6 (ordinal)								
Common time trend ³	xxxx	xx.xx (xx.xx to xx.xx)	0.xxx	0.xx	xxxx	xx.xx (xx.xx to xx.xx)	0.xxx	0.xx
Multiple imputations (MAR) ⁵	xxxx	xx.xx (xx.xx to xx.xx)	0.xxx		xxxx	xx.xx (xx.xx to xx.xx)	0.xxx	
Multiple imputations (+1) ⁶	xxxx	xx.xx (xx.xx to xx.xx)	0.xxx		xxxx	xx.xx (xx.xx to xx.xx)	0.xxx	
Multiple imputations (death) ⁷	xxxx	xx.xx (xx.xx to xx.xx)	0.xxx		xxxx	xx.xx (xx.xx to xx.xx)	0.xxx	
Varying time trends ⁴	xxxx	xx.xx (xx.xx to xx.xx)	0.xxx	0.xx	xxxx	xx.xx (xx.xx to xx.xx)	0.xxx	0.xx
NIHSS at Day 7 (ordinal)								
Common time trend	xxxx	xx.xx (xx.xx to xx.xx)	0.xxx	0.xx	xxxx	xx.xx (xx.xx to xx.xx)	0.xxx	0.xx
Varying time trends	xxxx	xx.xx (xx.xx to xx.xx)	0.xxx	0.xx	xxxx	xx.xx (xx.xx to xx.xx)	0.xxx	0.xx
NIHSS at Day 7 (continuous)								
Common time trend	xxxx	xx.xx (xx.xx to xx.xx)	0.xxx	0.xx	xxxx	xx.xx (xx.xx to xx.xx)	0.xxx	0.xx
Varying time trends	xxxx	xx.xx (xx.xx to xx.xx)	0.xxx	0.xx	xxxx	xx.xx (xx.xx to xx.xx)	0.xxx	0.xx
Poor outcome (mRS 3-6) at Month 6 (binary)								
Common time trend	xxxx	xx.xx (xx.xx to xx.xx)	0.xxx	0.xx	xxxx	xx.xx (xx.xx to xx.xx)	0.xxx	0.xx
Varying time trends	xxxx	xx.xx (xx.xx to xx.xx)	0.xxx	0.xx	xxxx	xx.xx (xx.xx to xx.xx)	0.xxx	0.xx
Death at Month 6 (binary)								
Common time trend	xxxx	xx.xx (xx.xx to xx.xx)	0.xxx	0.xx	xxxx	xx.xx (xx.xx to xx.xx)	0.xxx	0.xx
Varying time trends	xxxx	xx.xx (xx.xx to xx.xx)	0.xxx	0.xx	xxxx	xx.xx (xx.xx to xx.xx)	0.xxx	0.xx
Dependency at Month 6 (binary)								
Common time trend	xxxx	xx.xx (xx.xx to xx.xx)	0.xxx	0.xx	xxxx	xx.xx (xx.xx to xx.xx)	0.xxx	0.xx
Varying time trends	xxxx	xx.xx (xx.xx to xx.xx)	0.xxx	0.xx	xxxx	xx.xx (xx.xx to xx.xx)	0.xxx	0.xx
EQ-5D scores at Month 6								
Problems with mobility (ordinal)	xxxx	xx.xx (xx.xx to xx.xx)	0.xxx	0.xx				

Problems with self-care (ordinal)	xxxx	xx.xx (xx.xx to xx.xx)	0.xxx	0.xx				
Problems with usual activities (ordinal)	xxxx	xx.xx (xx.xx to xx.xx)	0.xxx	0.xx				
Problems with pain/discomfort (ordinal)	xxxx	xx.xx (xx.xx to xx.xx)	0.xxx	0.xx				
Problems with anxiety/depression (ordinal)	xxxx	xx.xx (xx.xx to xx.xx)	0.xxx	0.xx				
Overall health utility (continuous)	xxxx	xx.xx (xx.xx to xx.xx)	0.xxx	0.xx				
Time to hospital discharge (survival)								
Cox model	xxxx	xx.xx (xx.xx to xx.xx)	0.xxx	0.xx				
Place of residence at Month 6 (ordinal)								
Common time trend	xxxx	xx.xx (xx.xx to xx.xx)	0.xxx	0.xx				

- 1) For ordinal, continuous and binary outcomes, the unadjusted model consists in a generalised linear mixed model with a random effect for cluster (hospital site), a fixed effect indicating the group assignment of each cluster at each step and a fixed categorical effect of time (each step). Appropriate distributions and link functions are used depending on the nature of the outcome. For survival outcomes, we use a Cox model with a random cluster effect, a fixed categorical period effect as well as a binary variable indicating the group allocation during each period in each cluster.
- 2) Adjusted models include the following baseline covariates: aaaaa

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)
- the p-value in bold red indicates the main analysis of the primary outcome
- p-values in bold green indicate the main analysis of the 7 secondary outcomes, these will be subject to multiplicity adjustments using the Holm-Sidak correction

Table 11. SAEs

Event	Care Bundle (N =)	Usual Care (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%)	
<i>Etc. by descending frequency of body system and descending frequency of preferred term</i>			

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.

Table 12. Causes of death

Cause	Care Bundle (N =)	Usual Care (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%
Deaths related to COVID-19	N=XXX	N=XXX
Most common cause/association #1	nnn xx%	nnn xx%
Most common cause/association #2	nnn xx%	nnn xx%
Etc.		
Most common cause/association #10	nnn xx%	nnn xx%
All other causes/associations	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. The breakdown of COVID-19 deaths by cause/association will depend on the final numbers and might include less than 10 categories.

Table 13. Protocol violations and deviations

Cause	Care Bundle (N =)	Usual Care (N =)
Randomisation violations	N=XXX	N=XXX
Age <18 years	nnn xx%	nnn xx%
Acute stroke syndrome not primary ICH	nnn xx%	nnn xx%
Presentation >6 hours from last seen well	nnn xx%	nnn xx%
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%
Missing primary outcome	N=XXX	N=XXX
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 14. Form of assessment of 6-month outcomes

Cause	Care Bundle (N =)	Usual Care (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%

5.2 Figures

Figure 1. CONSORT diagram

Figure 2. Start and stop dates of each period with number recruited per site per country

Programming note: order by country and then by randomised group and then by start date

Figure 3. Systolic blood pressure over time

Programming note: Longitudinal mean plot with 95% confidence intervals. Display denominators (N) under the x-axis at key timepoints.

Figure 4. Diastolic blood pressure over time

Programming note: Longitudinal mean plot with 95% confidence intervals. Display denominators (N) under the x-axis at key timepoints.

Figure 5. Blood glucose over time

Programming note: Longitudinal mean plot with 95% confidence intervals. Display denominators (N) under the x-axis at key timepoints.

Figure 6. Body temperature over time

Programming note: Longitudinal mean plot with 95% confidence intervals. Display denominators (N) under the x-axis at key timepoints.

Figure 7. 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 8: Boxplot of hematoma volume by follow-up assessment**Figure 9: Boxplot of NIHSS by follow-up assessment****Figure 10. Forest plot for subgroup analysis of mRS at 6 months****Figure 11. 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.

Figure 12. Kaplan Meier curve of mortality over 6 months

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

5.3 Listings

Listing 1. Protocol deviations

Site ID	Patient ID	Date	Type of deviation	Description	Corrective action taken
6	6001	27-Sep-10			
	6008	20-Sep-10			
	6052	26-Jun-11			
	6054	21-Jun-11			

6 Proposed content and timing of primary and subsequent publications

N	2023
1	Main results paper: treatment effects of care bundle on primary and secondary efficacy and safety outcomes, and according to pre-specified subgroups
2	Further subgroup analysis: relation of treatment effects by time, ethnicity, age, and neurological severity
3	Further subgroup analysis: differential treatment effects by surgical management
4	Further subgroup analysis: differential treatment effects by baseline neurological severity
5	Overall and individual treatment effects on haematoma growth and perihematoma oedema
6	Effect of compliance including per-protocol analyses
	2024 and subsequent years
7	Treatment effects according to utility-weighted mRS scores
8	Association of achieved blood pressure and glucose levels and outcomes
9	Feasibility and cost-effectiveness of care bundle for ICH
10	Influence of specific surgical interventions on outcome from ICH – propensity score analysis
11	Accuracy of clinician predictions of outcome from ICH
12	Clinical and imaging predictors of poor outcome
13	Health economic analysis: estimating cost-effectiveness of the intervention
14	Patterns and predictors of major outcomes (death, recurrent ICH, coronary events, falls and re-admission to hospital) after ICH
15	Determinants of HRQoL and influence of age, sex, ethnicity, and level of disability
16	Regional determinants of presentation and treatment times in ICH
17	Regional variation in the management of intracerebral haemorrhage
18	Frequency, predictors, and prognostic significance of seizures after ICH
19	Patterns and determinants of antithrombotic and statin use after ICH
20	Relation of clinical profile to recovery patterns after ICH
21	Patterns of recovery according to mRS scores over 6 months follow-up
22	Clinical-radiological correlations of baseline imaging and clinical and pathological classifications
23	Inclusion of data in systematic reviews/meta-analyses including the Blood pressure in Acute Stroke Collaboration (BASC) and of brain imaging determinants of outcome