Appendix S1

Enchanted

Enhanced Control of Hypertension and Thrombolysis Stroke Study

STATISTICAL ANALYSIS PLAN

for the

blood pressure arm of this study

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1. Signatures

We confirm finalisation of the ENCHANTED BP arm SAP prior to unblinding of the data.

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The George Institute for Global Health,
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10 August 2018
Date

Signature

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10 August 2018
Date

Signature

2. List of abbreviations

AF	atrial fibrillation
AHA	American Heart Association
AIS	acute ischaemic stroke
BP	blood pressure
CD-ROM	compact disc read-only memory
CI	confidence interval
CONSORT	consolidated standards of reporting trials
CRF/eCRF	case report form / electronic case record form
CT	computerised tomography
CV	cardiovascular
DICOM	digital imaging and communications in medicine
DSMB	data safety monitoring board
ECG	electrocardiogram
ENCHANTED	ENhanced Control of Hypertension And Thrombolysis strokE stuDy
FDA	Food and Drug Administration
GCP	good clinical practice
GCS	Glasgow coma scale
HR	heart rate
HREC	human research ethics committee
HRQoL	health-related quality of life
ICC	international coordinating centre
ICH	intracerebral haemorrhage
ICH-GCP	international conference on harmonisation for good clinical practice
ie	id est, or that is
IQR	interquartile range
IRB	institutional review board
ITT	intent-to-treat
iv	intravenous
IVRS	interactive voice randomisation system
LTFU	loss to follow up
MedDRA	Medical Dictionary for Regulatory Authorities
mins	minutes
MIU	mega-international units
MRI	magnetic resonance imaging
mRS	modified Rankin scale
NB	nota bene, or note
NHMRC	National Health and Medical Research Council of Australia
NIHSS	National Institute of Health stroke scale
NINDS	National Institutes of Neurological Diseases and Stroke
OC	operations committee
OLR	ordinal logistic regression
OR	odds ratio

PI	principal investigator
PP	per-protocol
PT	preferred term
RCC/RCCs	regional coordinating centre / regional coordinating centres
rt-PA	recombinant tissue plasminogen activator
SAE	serious adverse event
SAP	statistical analysis plan
SBP	systolic blood pressure
SC	steering committee
SD	standard deviation
SE	standard error
sICH	symptomatic intracerebral haemorrhage
SOC	system organ class
SOP	standard operating procedures
TGI	The George Institute for Global Health
UK	United Kingdom
WHO	World Health Organisation

3. Study objectives

The ENCHANTED study involves an assessment of two parallel, active-comparison, interventional treatment arms – *dose of alteplase (recombinant tissue plasminogen activator [rtPA]) and intensity of blood pressure (BP) control* – on clinical outcomes in patients who fulfil standard eligibility criteria for intravenous (iv) thrombolytic therapy in acute ischaemic stroke (AIS). The alteplase dose arm has concluded, with publication of the study results in May 2016.[1]

The *primary aim* of the BP control arm is to evaluate whether, compared with the current guideline-recommended criteria for BP management (systolic BP [SBP] target <1180 mmHg), intensive BP lowering (SBP target range 130-140 mmHg) has *superiority* at improving functional outcome according to an ordinal comparison of the full range of scores on the modified Rankin scale (mRS) at 90 days (the corresponding null hypothesis is that there is no difference in outcome according to the different intensities of BP control).

The *key secondary aim* is to evaluate whether compared to current guideline recommended criteria for BP management, intensive BP lowering *reduces the harm* associated with any intracerebral haemorrhage (ICH) (the corresponding null hypothesis is that there is no difference in the rate of any ICH between groups of differing intensities of BP lowering).

Other secondary aims comprise examining the effects on symptomatic intracerebral haemorrhage (sICH); 'poor' functional outcome (mRS scores 2-6), death or major disability (mRS scores 3-6); separately on death and disability (mRS 3-5); early neurological deterioration; health-related quality of life (HRQoL); length of hospital stay; and need for permanent residential care.

Finally, there will be an exploration for any interaction in the treatment effect between intensive BP lowering and dose of alteplase.

4. Study design

4.1 Overview

ENCHANTED is an independent, investigator-initiated and conducted, international, multicentre, 2 x 2 partial factorial, prospective, open-label, assessor-blinded end-point (PROBE), randomised controlled trial that involves a package of 2 linked comparative treatment arms ('alteplase dose' and 'BP control'). The trial is being conducted in accordance with local and international regulatory and ethical requirements, and ICH-GCP. All participating hospitals received approval from required regulatory authorities, a human research ethics committee (HREC) or an institutional review board (IRB), prior to initiation of the trial. The rationale and design of the study have been described,[2] and the data will be reported in accordance with Consolidated Standards of Reporting Trials (CONSORT) statements for randomised trials.[3] The first patient was randomised in March 2012 and the last patient was randomised into the alteplase dose arm in August 2015, and into the BP control arm in April 2018. The trial was designed so that the treatment arms could be analysed separately: recruitment into the alteplase dose arm was much quicker than into the BP control arm,

necessitating the former completing earlier to the required sample size and the results reported in May 2016.[1] In brief, low-dose alteplase was not shown to be non-inferior to standard-dose alteplase with respect to death and disability at 90 days. However, low-dose alteplase was associated with significantly lower early mortality (at 7 days) and sICH. Moreover, low dose alteplase was non-inferior to standard-dose alteplase for the key secondary outcome of a shift (improvement) in functional outcome according to the full range of mRS scores at 90 days. The ENCHANTED trial is registered at the following sites: ClinicalTrials.gov (NCT01422616), ISRCTN Register (ISRCTN82387104); Australian New Zealand Clinical Trial Registry (ACTRN12611000236998); EU Clinical Trials Register (2011-005545-12); and Clinical Trials Registry – India (REF/2017/05/014334).

4.2 Patient population

To be eligible, patients with AIS were required to fulfil local criteria for use of iv alteplase, and the attending investigator clinician was required to sequentially consider their level of clinical uncertainty over the balance of benefits and risks pertaining to Arm B - the level of SBP control in each particular patient. Patients were ineligible if one or more of the following were noted: being unlikely to benefit from alteplase (e.g. advanced dementia); deemed to have a very high likelihood of death within the next 24 hours; have had another medical illness that was likely to interfere with the outcome assessment or follow-up (known significant pre-stroke disability, mRS scores 2-5); a specific contraindication of alteplase or any of the BP agents to be used; participation in another clinical trial involving evaluation of pharmacological agents; or need for the following concomitant medication (including phosphodiesterase inhibitors and monoamine oxidase inhibitors). Investigators were able to undertake all investigations according to their usual standard of care in their management of patients with AIS, including urgent referral for cerebral angiography for consideration of endovascular clot retrieval at selected sites. Thus, ENCHANTED is a pragmatic trial designed to evaluate routinely available thrombolytic treatment for AIS in usual best practice conditions.

Before participation, written consent was obtained from each participant or their approved surrogate for patients who are too unwell to comprehend the information. Study investigators may have withdrawn a patient from the trial at any time without prejudice and explanation. Although study participants/legally acceptable representatives can opt to withdraw at any stage, efforts are always undertaken to obtain outcome data.

4.3 Randomisation

After confirmation of eligibility, patients were randomised via a central password-protected web-based program developed at The George Institute for Global Health (TGI) in Sydney Australia. This was to ensure secure randomisation and concealment of treatment allocation. Registration and randomisation of each patient was achieved by connection to the study site. In China, investigators had the option of using a customised 24 hour digital IVRS that connected them to the central server to allow patients to be randomised at sites where rapid access to the internet was not possible.

A minimisation algorithm was used to achieve approximate balance in randomisation according to three key prognostic factors: (i) site of recruitment, (ii) time from the onset of symptoms (<3

versus ≥3 hours) and (iii) severity of neurological impairment according to the National Institutes of Health stroke scale (NIHSS)[4] score (<10 versus ≥10 points).

A fixed point randomisation sequence was used for the duration of the study. Initially, this occurred prior to administration of alteplase and within 4.5 hours of the onset of symptoms, as the randomisation allocation included treatment with low-dose versus standard-dose alteplase. At this time point, patients could also be randomised to different intensities of BP control. However, following the protocol amendment of 12 November 2013, the randomisation time point for the BP arm was extended to 6 hours from symptom onset to allow investigators greater flexibility in treating patients with alteplase as early as possible after symptom onset, as recommended in guidelines. After completion of the alteplase dose arm in August 2015, the randomisation system only allowed continued randomisation of patients into the BP arm.

Sixteen countries participated in the study: Australia, Brazil, Chile, Colombia, China, Hong Kong, India, Italy, Republic of Korea, Norway, Singapore, Spain, Taiwan, Thailand, UK, and Vietnam. However, the Republic of Korea did not participate in the BP control arm after conclusion of the alteplase dose arm.

4.4 Interventions and background care

Site investigators had the choice of randomising patients into one or both treatment arms of the study: Arm A randomised to standard-dose (0.9 mg/kg; 10% bolus and 90% infusion over 60 mins; maximum 90 mg) or low-dose (0.6 mg/kg; 15% bolus and 85% infusion over 60 mins; maximum 60 mg) iv alteplase (until August 2015); and Arm B randomised to intensive BP lowering (target SBP 130-140 mmHg within 60-minutes of randomisation, and to maintain this level for at least 72 hours, or hospital discharge [or death] if this occurs earlier) or guideline-recommended BP lowering (target SBP <180 mmHg) after the commencement of iv alteplase (throughout the ENCHANTED trial).

For Arm A alteplase dose, the bolus dose had been set to be similar for each treatment group; the only difference between groups was therefore in the total dose of alteplase. For Arm B, BP lowering was to be titrated by repeat iv bolus or infusion, with a SBP of <130 mmHg being the safety threshold for cessation of therapy. Since the trial seeks to address the impact of BP lowering, and not a specific agent, and to ensure the trial result is maximally generalisable to existing routine practice, flexibility was allowed in the use of locally available agents, though treatment protocols being based on available medications that are provided as appendices to the trial protocol.

All patients were to be managed in a facility with capacity for repeated neurological examination and non-invasive BP and heart rate monitoring (consistent recordings using automatic devices. The monitoring of these physiological measures was linked to administration of alteplase throughout the study, according to every 15 minutes for 1 hour, then hourly from 1 to 6 hours, then 6 hourly from 6 to 24 hours; then twice daily for 1 week [or hospital discharge or death, if earlier). All BP measurements were from the non-paretic arm (or right arm in situations of coma or tetraparesis), with the patient resting supine for ≥3 minutes. All patients were to receive active care and best practice management according to

guidelines, and where intra-arterial thrombolysis and/or endovascular mechanical clot retrieval was allowed, according to local practice.

An acute stroke unit is defined as an area that: is a geographically specific where patients with acute stroke are managed; has staff organised as part of a coordinated multidisciplinary team; has staff who have special knowledge and skills in the management of acute stroke; provides ongoing education about stroke management for staff, patients and caregivers; and has written protocols for assessment and management of common problems related to stroke.

4.5 Baseline and follow-up assessments

Each collaborating hospital site, except those located in the UK, was required to keep a screening log during the time of participation of all patients presenting with a diagnosis of AIS who were considered for the study but were subsequently excluded. The screening log was to record each patient's initials and date of admission together with a brief description of the main reason as to why he or she was not randomised. The log was used to monitor recruitment and identify specific barriers to randomisation of eligible patients. For the UK, all sites contribute to a continuous cycle of national audits, that includes the number of stroke admissions, proportion of patients eligible for thrombolysis, and the proportion of patients thrombolysed, reported on a quarterly basis. This database will be interrogated at the end of the study to assess the proportion of thrombolysis-eligible patients in the UK who are included in ENCHANTED during the study period.

A detailed list of the assessment schedule is contained in the study protocol[2] and clinical site manuals. Briefly, once informed consent was obtained, the responsible registered investigator clinician was able to randomise a patient through the secure web-based system after eligibility was confirmed. Data were entered for several key baseline clinical variables including vital signs and scores on the GCS and the NIHSS.[4] Socio-demographic and clinical history were then recorded on a baseline form and regular checks were made of BP and neurological function over the next 24 and 72 hours, and for 7 days in total, according to a standard protocol. BP was recorded every 15 minutes during the first hour, then hourly for 5 hours, then 6 hourly until 24 hours, and twice daily thereafter for the next 7 days or, until death or hospital discharge. Scores on the GCS and NIHSS were recorded at 24 and 72 hours (or at hospital discharge if earlier), and mRS scores were recorded at Day 7 (or at hospital discharge if earlier). All data on clinical status, treatment and care were recorded prospectively on special prepared worksheets, and subsequently transferred onto electronic case record forms (eCRFs) on the electronic database. All patients were followed daily for 1 week, and then at 28 and 90 days, unless death occurred earlier.

The 28 and 90 day evaluations were conducted in-person or by telephone, by a trained staff member at the local site who was not directly involved in the acute treatment of the subject and was blind to the treatment allocation. In cases where the 90-day assessments was performed by an unblinded assessor, the occurrence was tallied as a protocol violation and presented in the final study report; nevertheless, the submitted subjects' data will be used in the analyses.

The hospital coordinator at each collaborating site ensured completion of data. Investigators received modest reimbursement for their time involved in data collection and for local expenses

(eg printing, internet connection, purchase of medications, copying of brain imaging). Patients who do not receive the allocated randomised treatment or do not follow the protocol, were still followed up and analysed as per the 'intent-to-treat' (ITT) principle. Data collection was kept to a minimum to ensure rapid enrolment and follow-up of patients within the context of routine clinical practice.

4.6 Assessment of brain imaging

CT scans (or MRIs) were conducted according to standardised techniques at baseline (ie confirmation of diagnosis) in all patients, and at 24-36 hours in as many patients as possible according to usual clinical practice. Uncompressed digital CT, MRI and angiogram images were collected in DICOM format on a CD-ROM identified only with the patient's unique study number and uploaded by a special purpose-built web-based system for central analysis at TGI. The 24 hour analysed scans were used to assess for any ICH.

All scans with intracranial haemorrhage were assessed independently by at least two expert clinical scientists. If classification of the type of ICH was consistent between readers, the data were recorded directly to the database; if there was inconsistency, a third reader was required to review. Disagreement between the third reader and any of the former two readers prompted discussion within an adjudication committee to finalise the diagnosis and classification of ICH, according to the adjudication procedures outlined in Appendix 1.

The brain imaging system allowed assessment of abnormalities using computer-assisted multi-slice planimetric and voxel threshold techniques in MiStar version 3.2 (Apollo Medical Imaging Technology, Melbourne, Victoria, Australia). The system was built to store securely over 10,000 images acquired on participants, with an adjudication system primarily for the recording of ICH. A more sophisticated system is being developed for future analysis of cerebral ischaemia using a validated process of recording: (i) *acute ischaemic signs* that includes the presence and degree of hypoattenuated tissue ('mild' = grey matter attenuation equal to normal white matter; 'severe' = grey and white matter attenuation less than normal white matter), acute ischaemic lesion extent, ischaemic lesion swelling (seven-point scale), presence/absence and location of any hyperattenuated artery; and (ii) *pre-existing ('brain frailty') signs* that includes old infarcts (cortical, lacunar, border zone, brainstem/cerebellar), presence/severity of leukoaraiosis, and cerebral atrophy against standard examples.

4.7 Sample size and statistical power for the BP control arm

Primary endpoint: The power calculations for the ENCHANTED BP arm were initially based on the estimated treatment effects on a conventional binary assessment of 'poor clinical outcome', defined as death or disability according to scores 3-6 on the mRS. The SITS-ISTR registry indicates that a $\geq$15mmHg SBP difference between randomised groups (i.e. 130-140 mmHg vs. 180 mmHg SBP targets) could be associated with a $\geq$15% reduction in poor outcome in patients who receive standard-dose alteplase.[5] However, assuming a potential interaction between low-dose alteplase and intensive BP lowering, a more conservative 13% reduction in poor outcome was expected in patients who received low-dose alteplase in combination with intensive BP lowering. Assuming event rates of 50% in the guideline-based BP lowering group and 43% in the intensive BP lowering group, a sample size of 2304 (1152 per group) was

estimated to provide >90% power (using a two-sided α=0.05) to detect a 14% relative reduction in the poor outcome in the intensive BP lowering group, with 5% drop-out.

However, during the course of the trial, the primary outcome for the BP control arm was changed to an ordinal shift in the analysis of the full range of the mRS at 90 days. This is because the ordinal shift approach had gained greater recognition as a meaningful assessment of patient recovery in terms of physical functioning by the clinical, scientific and regulatory community, as exemplified by it being used in all the trials of endovascular treatment in AIS.[6,7] As well as providing greater relevance to assessing recovery from this critical and disabling illness, the ordinal shift analysis provides efficiency gains by decreasing the required sample size. Re-estimation of the sample size based on ordinal anlaysis of the mRS suggested the estimated treatment effect could be detected with a sample size of 2100.

Key secondary outcome: In the Cochrane review, the overall risk of any ICH following standard-dose alteplase was 23%.[8] Observational studies of Japanese patients who had received low-dose alteplase suggest lower risks of any ICH (17%, risk reduction 23%).[9-11] Based on the SITS-ISTR registry,[5] an expected 15mmHg difference between randomised groups of SBP lowering is likely to be associated with a ≥40% reduction in any ICH in those who receive standard-dose alteplase. Assuming a potential interaction between low-dose alteplase and intensive BP lowering, a more conservative 36% reduction is expected in patients who receive low-dose alteplase. With an average 20% rate of any ICH among patients who receive guideline-based BP lowering and 12.3% among those with intensive BP lowering, the study will provide >90% power (two-sided α=0.05) to detect reductions in any ICH from intensive BP lowering, with a 5% drop-out. The study will also examine the effects of the treatment on sICH according to various standard definitions. With an expected rate of 3-6%, this sample size will allow an exploration of the treatment effect across the various definitions of sICH.

A total of 939 patients participated in the combined Arms A and B.

4.8 Unblinding

In accordance with standard operating procedures (SOP) of TGI, the number of people having access to the interim data/results was kept to a minimum, and only included members of the Data and Safety Monitoring Board (DSMB) and associated statisticians responsible for writing the reports. Statisticians not involved in the writing of the DSMB reports remain blinded until the final study results are released, and work on dummy datasets to develop, and test, the statistical computer code. Treatment allocations are stored securely in a separate location to other data for this purpose.

The SAP was written by the principal investigator, two independent statisticians, and several other investigators, who will remain blind to the treatment allocations and study results until the final study results are released.

4.9 Definition of outcomes

4.9.1 Primary outcome

The primary outcome is shift ('improvement') in measures of function according to the full range of scores on the mRS at 90 days after randomisation.[12-14] Ordinal approaches to analysis

of the mRS are increasingly being used to appreciate the effects of medical[4,15] and endovascular reperfusion therapies[16-18] in patients with AIS, and to improve statistical efficacy. The mRS,[19,20] is the most widely used instrument for grading the impact of stroke treatments, that assesses daily functioning through the categorisation of levels of disability (or 'dependency', sometimes equated to 'handicap'). The broad mRS scaling is: 0 = no symptoms at all; 1 = no significant disability despite symptoms, but able to carry out all usual duties and activities; 2 = slight disability, unable to carry out all previous activities but able to look after own affairs without assistance; 3 = moderate disability requiring some help, but able to walk without assistance; 4 = moderate-severe disability, unable to walk without assistance and unable to attend to own bodily needs without assistance; 5 = severe disability, bedridden incontinent, and requiring constant nursing care and attention; 6 = dead.

4.9.2 Other efficacy outcomes

The occurrence of a poor outcome at 90 days after randomisation will be assessed with the conventional dichotomous analysis of the mRS, as used in the National Institute of Neurological Disorders and Stroke (NINDS) trial.[21] The protocol states that scores of 2–6 (i.e. death or disability) are defined as a poor outcome and scores of 0-1 as an 'excellent outcome'. Scores of 0-2 are defined as a 'good outcome'.

4.9.3 Analysis of efficacy outcomes

The primary analysis of the mRS will be unadjusted, undertaken using a shift in measures of functioning according to the full range of mRS scores, and analysed using ordinal logistic regression (OLR). OLR assumes proportionality of odds, which will be tested using a likelihood ratio test. The effect of intensive versus guideline-recommended BP control will be summarised by an odds ratio (OR) and 95% confidence interval (CI). The Howard method[14] will also be used as a sensitivity analysis to describe the distribution of categories on the mRS. A further sensitivity analysis will be undertaken, using logistic regression, with adjustment for the minimization variables, including NIHSS as a continuous variable, and several other prognostic covariates: age, sex, ethnicity, pre-morbid mRS (0 or 1), pre-morbid use of antithrombotic agents (aspirin, other antiplatelet agent or warfarin), and history of stroke, coronary artery disease, diabetes mellitus, and atrial fibrillation (AF), and randomised alteplase dose.

The primary analysis of the treatment effect on the secondary efficacy outcomes (the conventional dichotomous (i.e. 0-1 versus 2-6 separation of the mRS) will also be unadjusted. A further sensitivity analysis will be undertaken using the same covariates as outlined above, in an adjusted analysis.

4.9.4 Key safety outcomes

The safety outcomes are any ICH and sICH, defined in various ways. Any ICH is defined as ICH of any type on brain imaging ≤7 days of treatment, identified by adjudicators; and sICH is defined according to the following criteria:

- the Safe Implementation of Thrombolysis in Stroke-Monitoring Study (SITS-MOST),[22] as large local or remote parenchymal ICH (type 2, defined as greater than 30% of the infarcted

area affected by haemorrhage with mass effect or extension outside the infarct) combined with neurological deterioration (≥4 points on the NIHSS) or leading to death within 24-36 hours;

- the NINDS trial[21] criteria of any ICH associated with neurological deterioration (≥1 point change in NIHSS score) from baseline or death within 24-36 hours;
- the European-Australian Cooperative Acute Stroke Study 2 (ECASS2)[23] of any ICH with neurological deterioration (≥4 points on the NIHSS) from baseline or death within 24-36 hours;
- the ECASS3[24] trial of any ICH with neurological deterioration (≥4 points increase on the NIHSS) from baseline or death within 36 hours;
- the International Stroke Trial 3[25] of either significant ICH (local or distant from the infarct) or significant haemorrhagic transformation of an infarct on brain imaging with clinically significant deterioration or death within the first 7 days of treatment;
- clinician-reported ICH as a serious adverse event (SAE);
- fatal ICH, defined by any parenchymal ICH of type 2 and death within 7 days.

4.9.5 Other secondary outcomes

Other secondary outcomes will comprise the following:

- Cause-specific mortality within the 90-day follow-up period. The primary cause of death will be categorised as:
  - death from direct effects of the initial AIS (within 7 days unless there is a definite alternative cause);
  - death from pneumonia or other complications of the AIS (beyond 7 days unless there is a definite alternative cause;
  - death from a serious cardiovascular (CV) event other than acute stroke;
  - death from recurrent acute stroke;
- Death or major disability, according to scores 3-6 on the mRS;
- Death or neurological deterioration (≥4-points decline in NIHSS) within 24 hours;
- Duration of initial hospitalisation in days;
- Health-related quality of life (HRQoL), as assessed on the EuroQoL,[26] as an overall health utility score (ED-5D-3L) at 90 days.

4.9.6 Tertiary outcomes

Tertiary outcomes will include the following:

- All-cause mortality at 7 and 28 days;
- Place of death (in initial acute hospital, another hospital or institutional facility, at home);
- Trends in physical functioning on the mRS over 7, 28 and 90 days;
- Duration of stay in an intensive care unit;
- Treatment effects according to the use of endovascular clot retrieval therapy;

- Separate components of the EQ-5D - mobility, self-care, usual activities, pain/discomfort, and anxiety/depression - at Days 28 and 90.

4.9.7 Safety variables

All deaths and ICH are adjudicated by a blinded central expert committee. Since all patients have AIS, deaths are classified as being due to this condition within 7 days, unless an unequivocal non-cerebral cause was established. SAEs are reported according to standard definitions and coded using terminology of the Medical Dictionary for Regulatory Authorities (MedDRA). However, as this a classification by System-Organ Class (SOC) and Preferred Term (PF) that are not necessarily relevant for this study, the following categories of SAEs derived from MedDRA are defined:

- Neurological deterioration as a direct effect of the AIS with or without evidence of mass effect or ICH on repeat brain imaging;
- Major extracranial haemorrhage;
- Recurrent AIS with the onset of focal neurological symptoms and signs consistent with acute stroke occurring more than 24 hours after the primary event without alternative diagnosis explained on repeat brain imaging;
- Recurrent AIS with neurological symptoms and signs consistent with acute stroke and brain imaging has excluded ICH and non-stroke lesion;
- Recurrent acute stroke syndrome without confirmatory brain imaging or necropsy;
- Acute coronary event according to standard definitions consistent with a typical clinical presentation, abnormal electrocardiogram, or abnormally elevated enzymes;
- Other CV event including sudden death.

SAEs will be further categorised into fatal and non-fatal SAEs, with a similar structure.

4.9.8 Protocol violations

Patients who have one or more of the following protocol violations will be excluded from the per-protocol (PP) population: age <18 years; final diagnosis not AIS; systolic BP >185 mmHg (inclusion criteria BP level); randomised >6 hours of onset; final diagnosis unknown/uncertain because of missing source documents or neuroimaging; failure to receive alteplase; failure to receive randomised BP lowering treatment and failure to obtain a blind assessment of the 90-day outcome.

5. Funding

The main source of funding for the study is from the National Health and Medical Research Council (NHMRC) of Australia (Project Grant numbers 1020462 and 1101113). Other sources of funding are from the Stroke Association of the UK (Reference TSA 2012/01 and 2015/01), the National Council for Scientific and Technological Development of Brazil (CNPq grant number 467322/2014-7), and Takeda for conduct of the study in China. The sponsors of the study had no role in study design, data collection, data analysis, data interpretation, or writing

of the report. The corresponding author will have full access to all the data in the study and takes final responsibility of the decision to submit the SAP for publication.

6. Statistical analysis

6.1 Analysis principles

- Analyses will be conducted on an intention-to-treat (ITT) basis.
- A sensitivity per-protocol (PP) analysis will also be carried out on patients who fulfil inclusion criteria with definite AIS who achieved the target SBP within 60 minutes of the bolus of alteplase into the BP arm and had a 90-day blinded outcome assessment.
- Analysis of the primary and secondary endpoints will be for the superiority of guideline versus intensive BP lowering. All tests are two-sided and the nominal level of α will be 5%.
- The primary analysis of the treatment effects on all outcomes will be unadjusted.
- Sensitivity analyses of the treatment effects on all outcomes will adjust for the minimisation and key prognostic covariates of age, sex, ethnicity, pre-morbid mRS, pre-morbid use of an antiplatelet agent (aspirin or other antiplatelet agent), and history of stroke, coronary artery disease, diabetes mellitus and AF, and for low-dose versus standard-dose alteplase.
- Adjusted analyses will also include multiple imputation by chained equations with 30 imputations, should the number of missing observations be substantial (>10%). The number of observations used in such analyses will be reported. Last observations will not be carried forward unless this is necessary.
- Heterogeneity of treatment on outcomes will be assessed in subgroups: age (<65 vs. ≥65 years), sex (male vs. female), ethnicity (Asian vs. non-Asian), time to randomisation (<3 vs. ≥3 hours), baseline SBP (above vs. below median), history of hypertension, NIHSS at baseline (above vs. below median), final diagnosis of AIS subtype, antiplatelet agent used, and randomised alteplase dose. Tests of the null hypothesis of homogeneity will be carried out by fitting multivariable OLR models, including the main and interaction effects of each of the subgroup variables, with the BP intervention indicator variable, in turn.
- Subgroup analyses will be carried out irrespective of whether there is a significant treatment effect on the primary outcome. These analyses will be adjusted for the minimisation and key prognostic covariates of age, sex, ethnicity, pre-morbid mRS, pre-morbid use of aspirin/other, and history of stroke, coronary artery disease, diabetes mellitus and AF, and randomised alteplase.
- The primary subgroup analysis is that for alteplase dose, since this examines the interaction effect of the two randomised interventions. Consequently, this subgroup will be explored in greater detail by obtaining ORs for each other possible yes/no combination of the two interventions relative to the group who were randomised to both control therapies. Such analyses will be performed for all outcomes using logistic, OLR or least squares regression

model, as appropriate for ordinal, binary and continuous outcomes (after transformation if necessary), respectively, and presented in tabular form.

- No formal adjustments to the P values will be applied to allow for multiplicity. The purpose of secondary, sensitivity and subgroup analyses is to supplement evidence of the primary analysis of the treatment effect. However, the results will be interpreted in this context.
- Analyses will be conducted primarily using SAS software.

6.2 Interim analyses

An independent Data Safety Monitoring Board (DSMB) (Chair, Professor John Simes of the Clinical Trials Centre, University of Sydney), and consisting of clinicians and biostatisticians, reviewed unblinded data from the ENCHANTED study at twice-yearly intervals during conduct of the trial. The DMSB Charter outlined the need to review recruitment, BP separation, dropout and event rates, monitor safety endpoints, and examine the effect of treatment on efficacy outcomes. They were also charged with informing the study Steering Committee (SC) and Operational Committee (OC) if at any time there emerges either evidence beyond reasonable doubt of a difference between randomised groups in the primary outcome, or evidence that is likely to change clinical practice in the context of current knowledge.

Two formal interim analyses after approximately 33% and 66% of the patients had been followed-up for 30 days were planned and actually conducted. The Haybittle-Peto stopping rule was used (i.e. a difference 3 SE is considered to be clear evidence of a treatment effect). The study was not terminated early and no additional looks to the discretion of the DSMB were added. The final last level of significance with 3 looks will therefore be 0.0482. Although naïve estimates can theoretically be slightly biased when a stopping rule is used, there will be no correction of the estimates on termination as the bias is likely to be negligible with this design.

6.3 Dates, vital status and consent-related issues

The study is conducted at sites with experience in acute stroke care. Regionally-based experienced clinical research monitors perform online and on-site data verification; site monitoring is undertaken, initially after the first few patients were randomised at sites, and thereafter the frequency of monitoring was determined by patient recruitment numbers and data quality whilst site staff continued to participate in the trial. As this is an open trial of differing management strategies in a critical illness, monitoring serves to confirm that investigators adhere to the protocol and ICH-GCP guidelines, and the accuracy of the data. Site monitoring was to confirm: (i) demographic and consent details on all randomised patients; (ii) details of all SAEs against source documents; (iii) details of all mRS score against source documents; (iv) collect/correct any outstanding/missing data; and (v) check selected variables against source medical documents in approximately 10% random selection of patients. Key data points, vital status at final follow-up, dates and details of any deaths are queried in order for no missing values to remain at the end of the study.

Two important situations may have led to the cessation of participation in the study: a patient, next of kin or legal surrogate may have withdrawn consent; or they may have refused continuation of the study treatment when delayed consent was sought. For both situations, the study treatment was ceased and the patient receive appropriate treatment as determined by the attending clinician. The information statement provided to the patient and/or the next of kin or surrogate clearly states that the patient can be withdrawn from the study at any time without prejudice and explanation. Such withdrawal is documented in the patient's file. If withdrawal of consent relates to the study treatment alone, data collection continued on documentation of this fact in the patient's files. If consent for use of data was withheld, the patient's data was removed from analyses, except for data related to consent. Censoring dates will be used only in cases of 'real' loss-to-follow-up (LTFU), such that the date of censoring will be the last day of contact, or the date of hospital discharge, if not other information is available.

In cases where the 90-day assessments were performed by an unblinded assessor, as assessed by requesting knowledge of the assessor at follow-up, such occurrences will be tallied as protocol violation and presented in the final study report: nevertheless, the submitted subjects' data will be used in the analyses.

6.4 Trial profile

Flow of patients through the study will be displayed in a CONSORT diagram, shown in the Appendix 2 (Figure 1). The report will include: the number of screened patients who met study inclusion criteria and the number of patients who are included; and reasons for exclusion of non-included patients and accompanying information. In addition, the number of patients randomised outside the time window and other protocol deviations will be provided, as outlined in Appendix 3 (Table 1).

6.5 Data sets analysed

- ITT population - the data set of *all patients randomised* in the study without exclusion and the analysis conducted according to the ITT principle. This will be used to assess both efficacy and safety.
- Analysed data set - includes data from all randomised patients in the study who are known to have died or with mRS scores at 90 days.
- PP population – the data set includes all randomised participants with the primary outcome recorded and who did not have a relevant protocol violation.

6.6 Patients characteristics and baseline comparisons

Description of the following baseline characteristics will be presented by treatment group as outlined in Appendix 2 (Table 1). Discrete variables will be summarised by frequencies and percentages. Percentages will be calculated according to the number of patients in whom data are available. If missing values are important, the denominator will be added in a footnote in the corresponding summary table. In some instances, frequencies and percentage of patients in subcategories of variables will be reported, for example by age (10-year strata), region (by

country of recruitment) and time from stroke onset to randomisation (1 hour strata) (Appendix 3, Table 2).

Continuous variables will be summarised by use of standard measures of central tendency and dispersion, either mean and SD for variables identified with #, or median and interquartile range (IQR) with †. Durations will also be summarised by medians and IQR.

Baseline measures for all patients will be tabulated for the following variables: age #, sex, ethnicity (Asian vs. other), geographical region (China, other Asia, Australia/Europe, and South America), SBP #, diastolic BP #, heart rate #, NIHSS score †, GCS score †, medical history (prior stroke, hypertension, coronary heart disease, AF, diabetes mellitus, and smoking status), time between onset and randomisation †, medications at time of admission, final diagnosis of presumed pathological type of AIS, and presence of cerebral infarction.

6.7 Process measures of background management and treatment

This will be described as outlined in Appendix 2 (Table 2). Counts and percentages will be calculated per treatment arm for all items of standard stroke care. The period covers Day 0 (randomisation) to Day 7. A P value from a χ^2 test or Fisher test will also be reported. The default analysis is based on the χ^2 test unless any expected number per cell is <5, in which case a Fisher test will be used.

6.8 Alteplase details after randomisation

As 939 participants were additionally randomised to the dose arm, alteplase details will also be outlined in Appendix 2 (Table 2). Details of the time to treatment, and bolus and infusion doses of alteplase will be summarised by treatment arm. Counts and percentages will be displayed for all categorical items. Continuous outcomes will be summarised by either means (SD) or medians (IQR) as further detailed in the same table.

6.9 BP management

Details on SBP and diastolic BP (DBP) from the time of use of the bolus of alteplase will be outlined in a Table and Figure. The same measures will also be recorded from the time of initiation of BP lowering, and outlined in a Table and a Figure.

6.10 Primary and secondary outcomes

The primary analysis of the effect of treatment on the primary measure of functional recovery will be based on unadjusted OLR across all levels of the mRS at 90 days. This analysis assumes a common OR across all cut points of the mRS. A shift figure will be presented to illustrate the change distribution across treatment arm. If the proportional odds assumption is violated in either of these analysis (i.e. significant P value for the Brant test of common OR a model with non-proportional odds will be fitted. A standard χ^2 test will be used as the primary test of statistical significance on the effect of treatment allocation on functional outcome. Frequencies and % per arm, and an OR measuring the treatment effect and its 95% CI will also be reported. We will also perform adjusted analyses for sensitivity purposes. They will be based on a multivariable OLR model adjusted for randomisation strata and key prognostic covariates: age,

sex, ethnicity, pre-morbid mRS (0 or 1), pre-morbid use of aspirin/other antiplatelet agent, and any history of stroke, coronary artery disease, diabetes mellitus, AF, and randomised alteplase dose. If the missing data exceed 10%, multiple imputations will be performed. If there are notably different conclusions from the analysis based on approaches to analysis of the mRS, the reasons for such differences will be explored in secondary analysis to be published after the primary paper. The primary analysis of the effect of treatment on the key secondary efficacy outcome of poor outcome will be undertaken using the traditional dichotomous (i.e. 0-1 versus 2-6) separation of the mRS, as outlined in Appendix 2 (Table 3). The interaction between alteplase dose and intensity of BP lowering on the shift in mRS score will be displayed (in Appendix 2, Table 4 and Figure 4)

6.11 Other secondary outcomes

All binary secondary outcomes will be analysed by means of a χ^2 test, except that a Fisher test will be used if any expected numbers are <5. These data will be summarised by an OR and its 95% CI as before. The effect of treatment on survival time or any time-to-event type of outcome will be tested by means of a log-rank test. Continuous endpoints, such as the health utility score (ED-5D) at 90 days, will all be summarised by medians (IQR). A difference between medians and its 95% CI might be computed if this is feasible and required in subsequent publications. Probability of survival by treatment group may be presented as Kaplan-Meier curves. Length of stay in hospital and in an intensive care unit will be censored due to early deaths or stays longer than 90-days (Appendix 2, Table 5); they will therefore be considered as times to discharge and analysed with a log-rank test.

6.12 Safety endpoints

Counts and percentages per treatment arm will generally be summarised as all specific pre-defined SAE categories, as outlined in Appendix 2 (Table 6). These generally represent the number of patients experiencing a specific SAE (at least once), fatal ones, and the breakdown by subcategory (when appropriate). This includes evidence of an early neurological deterioration within 24-36 hours, the various forms of vascular and non-vascular events (i.e. pneumonia, sepsis, and fracture). A global chi-square (or Fisher test, if any expected value is <5) of a treatment effect will be carried out and its P value reported. A measure of treatment effect (i.e. OR and its 95% CI) might be reported if appropriate. None of the above analyses will be adjusted. A similar breakdown of the SAEs stratified by fatal/nonfatal status will also be presented. In addition, a table displaying all-cause mortality after the first 7 days and the primary cause of death (globally and per category) may be provided. All deaths occurring during the first week will be considered as stroke deaths unless otherwise specified. The same rules for the tests, OR and 95% CI apply.

6.13 Subgroup analysis

Analysis of 10 key subgroups will be carried out for the primary outcome, outlined in Appendix 2 (Table 7). Adjusted p-values will be reported. The pre-specified subgroup analyses are as follows:

1. Age: <65 versus ≥65 years

2. Sex: male versus female
3. Ethnicity: 'Asian' (i.e. Chinese or other Asian) versus 'non-Asian' (i.e. by groups defined as African, Arabic, Australian, Caucasian/European, Indian subcontinent, Maori/Polynesian, Mixed, and Latin American)
4. Time to from symptom onset to randomisation: <3 versus ≥3 hours
5. SBP at baseline: below and above mean
6. History of hypertension: yes/no
7. Baseline NIHSS score: above and below overall median
8. Final diagnosis of AIS at the time of hospital separation:
    - Large artery occlusion/stenosis on extra– or intra-cranial atheroma
    - Small vessel or perforating vessel 'lacunar' disease
    - Cardio-embolic
    - Other definite or uncertain pathological diagnosis
9. Pre-morbid use of aspirin or other antiplatelet therapy: yes/no
10. Dose of alteplase: low vs. standard

The cut points for continuous variables have been chosen by reference to an analysis of baseline characteristics (both treatment groups combined), so as to maximise power.

The main analysis for each subgroup will be an interaction test in a OLR model to determine whether the effect of treatment differs significantly across categories for that particular subgroup. Summary measures could include counts, percentages and a measure of effect size (OR) with its 95% CI obtained from a stratified analysis.

For the alteplase dose subgroup analysis, all endpoints will be analysed. The change in log likelihood when the interaction term is added to the relevant model containing the treatment and subgroup main effects will be calculated. The significance of the interaction will be assessed by comparing the change in log likelihood with percentage points of a χ^2 distribution with the appropriate degrees of freedom (a likelihood ratio test). The test is for the null hypothesis that all levels have the same underlying OR versus the alternative that the OR have a linear trend (if the levels are ordered), or simply that the OR are not all equal (if the levels are not ordered).

Subgroup results will be presented as forest plots, with P values for heterogeneity for each pair of subgroups.

6.14 Tables and figures

These are outlined in Appendix 2. Table 1 will report all collected baseline characteristics of the participants by treatment group. Table 2 will report on the use of alteplase (bolus and infusion dosage, and the times from randomisation and stroke onset to treatment) and BP management (time, treatment approaches, and mean achieved SBP over 24 hours). This table will also report on process measures, other concomitant treatments and details of management. Table 3 will display the results for primary and several secondary outcomes. Table 4 will present equivalent results for those who were randomised to both study arms. Table 5 will show findings for other secondary outcomes, and selected relevant tertiary outcomes. Table 6

will report SAEs to the end of follow-up. Subgroup analyses are presented in Table 7 and with a forest plot.

In addition, the following figures will be prepared:

- A CONSORT diagram illustrating the flow of patients through the study (Figure 1).
- A bar chart displaying each grade on the mRS in each treatment group (Figure 2).

7. Outline of publication plan

Appendix 4 outlines the proposed papers and their anticipated timelines for analysis of the ENCHANTED BP control arm of the study.

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Appendix 1

Adjudication and classification of intracerebral haemorrhage on brain imaging

Clinician scientists provide responses to the following questions:

1. Is there any evidence of haemorrhage on this scan? Yes/No

   If No, proceed to question 3

   If Yes, code bleeding as follows:

   a. HI1 Small petechiae along the margins of the infarct Yes/No

   b. HI2 Confluent petechiae within infarcted area but no space occupying effect Yes/No

   c. PH1 Blood clots in <30% of infarcted area with slight space-occupying effect Yes/No

   d. PH2 Blood clots in >30% of infarcted area with substantial space-occupying effect Yes/No

   And respond to following:

   Haemorrhage in region outside area of cerebral ischaemia/infarction'

   a. Subarachnoid Yes/No

   b. Intraventricular Yes/No

   c. Subdural Yes/No

   d. Other Yes/No

2. In your opinion, will this haemorrhage have been the predominant cause of the neurological worsening? Yes/No

3. Assessment of swelling.

   Is there any evidence of midline shift Yes/No

Abbreviations: HI denotes haemorrhagic infarction; PH, parenchymal haemorrhage

Appendix 2

Proposed format of data tables and figures for main results publication

Table 1: Baseline characteristics

	Intensive group (n=xxx)	Guideline group (n=xxx)
Time from stroke onset to randomisation (hrs:mins), mean (SD) and median (IQR)	xxx (xx)	xxx (xx)
Male, n (%)	xxx (xx)	xxx (xx)
Age (years), mean (SD)	xxx (xx)	xxx (xx)
median (iqi)	xxx (xx)	xxx (xx)
≥80**,** n (%)	xxx (xx)	xxx (xx)
Asian ethnicity n (%)	xxx (xx)	xxx (xx)
Clinical features		
Systolic BP (mmHg), mean (SD)	xxx (xx)	xxx (xx)
Diastolic BP (mmHg), mean (SD)	xxx (xx)	xxx (xx)
Heart rate (beats per minute), mean (SD)	xxx (xx)	xxx (xx)
NIHSS score		
Median (IQR)	xxx (xx)	xxx (xx)
≥14 (n, %)	xxx (xx)	xxx (xx)
GCS score		
Median (IQR)	xxx (xx)	xxx (xx)
Severe (3-8), n (%)	xxx (xx)	xxx (xx)
Medical history		
Hypertension, n (%)	xxx (xx)	xxx (xx)
Currently treated hypertension, n (%)	xxx (xx)	xxx (xx)
Previous stroke (ischaemic, haemorrhagic or uncertain), n (%)	xxx (xx)	xxx (xx)
Coronary artery disease, n (%)	xxx (xx)	xxx (xx)
Other heart disease (valvular or other), n (%)	xxx (xx)	xxx (xx)
Evidence of atrial fibrillation, n (%)		
Definite history of atrial fibrillation n (%)	xxx (xx)	xxx (xx)
Atrial fibrillation confirmed on ECG, n (%)	xxx (xx)	xxx (xx)
Diabetes mellitus, n (%)	xxx (xx)	xxx (xx)
Hypercholesterolaemia, n (%)	xxx (xx)	xxx (xx)
Current smoker, n (%)	xxx (xx)	xxx (xx)
Pre-stroke function (mRS), n (%)		
0 no symptoms	xxx (xx)	xxx (xx)
1 no significant disability	xxx (xx)	xxx (xx)
Medications at time of admission		
Antihypertensive agent(s), n (%)	xxx (xx)	xxx (xx)
Warfarin anticoagulation, n (%)	xxx (xx)	xxx (xx)
Aspirin or other antiplatelet agent, n (%)	xxx (xx)	xxx (xx)
Statin or other lipid lowering agent, n (%)	xxx (xx)	xxx (xx)
Brain imaging features*		
CT scan used, n (%)	xxx (xx)	xxx (xx)
MRI scan used, n (%)	xxx (xx)	xxx (xx)

Visible early ischaemic changes, n (%)	xxx (xx)	xxx (xx)
Visible cerebral infarction, n (%)	xxx (xx)	xxx (xx)
Visible cerebral infarction with mass effect, n (%)	xxx (xx)	xxx (xx)
CT or MR angiogram show proximal occlusion, n (%)	xxx (xx)	xxx (xx)
Final diagnosis at time of hospital separation		
Non-stroke, n (%)	xxx (xx)	xxx (xx)
Presumed stroke pathology, n (%)		
Large artery occlusion due to significant atheroma	xxx (xx)	xxx (xx)
Small vessel or perforating vessel lacunar disease	xxx (xx)	xxx (xx)
Cardio-embolic	xxx (xx)	xxx (xx)
Other or uncertain aetiology	xxx (xx)	xxx (xx)

*Data based on clinician reported findings. Detailed analysis of brain imaging through central expert review to be undertaken in separate papers

Table 2: Use of alteplase and BP and other management from randomisation to Day 7

	Intensive (n=xxx)		Guideline (n=xxx)		P value
Alteplase treatment					
Any given, n (%)	xxx	(xx)	xxx	(xx)	0.xxx
Bolus dose (mg), mean (SD)	xxx	(xx)	xxx	(xx)	0.xxx
Infusion over 60 mins dose (mg), mean (SD)	xxx	(xx)	xxx	(xx)	0.xxx
Patients outside dose range, n (%)	xxx	(xx)	xxx	(xx)	0.xxx
Time from randomisation to treatment (mins), median (IQR)	xxx	(xx - xx)	xxx	(xx - xx)	0.xxx
Time from stroke onset to treatment (mins), median (IQR)	xxx	(xx - xx)	xxx	(xx - xx)	0.xxx
BP management					
Any given in first 24 hours, n (%)	xxx	(xx)	xxx	(xx)	0.xxx
Time from alteplase bolus to treatment (mins), median (IQR)	xxx	(xx - xx)	xxx	(xx - xx)	0.xxx
Time from randomisation to treatment (mins), median (IQR)	xxx	(xx - xx)	xxx	(xx - xx)	0.xxx
Time from stroke onset to treatment (mins), median (IQR)	xxx	(xx - xx)	xxx	(xx - xx)	0.xxx
<4 hrs, n (%)	xxx	(xx)	xxx	(xx)	
≥4 hrs, n (%)	xxx	(xx)	xxx	(xx)	
Method of iv treatment, n (%)					
Bolus	xxx	(xx)	xxx	(xx)	
Infusion	xxx	(xx)	xxx	(xx)	
Number of iv agents, n (%)					
1	xxx	(xx)	xxx	(xx)	
2	xxx	(xx)	xxx	(xx)	
≥3	xxx	(xx)	xxx	(xx)	

Systolic BP over 24 hours, mmHg, mean (SD)	xxx	(xx)	xxx	(xx)	0.xxx
Any iv BP lowering treatment in days 2-7, n (%)	xxx	(xx)	xxx	xx	0.xxx
Management					
Endovascular clot retrieval used, n (%)	xxx	(xx)	xxx	xx	0.xxx
Intubation and ventilation, n (%)	xxx	xx	xxx	xx	0.xxx
Fever occurrence, n (%)	xxx	xx	xxx	xx	0.xxx
Fever treated, n (%)	xxx	xx	xxx	xx	0.xxx
Nasogastric feeding given, n (%)	xxx	xx	xxx	xx	0.xxx
Patient mobilised by therapist, n (%)	xxx	xx	xxx	xx	0.xxx
Compression stockings used, n (%)	xxx	xx	xxx	xx	0.xxx
Subcutaneous heparin used, n (%)	xxx	xx	xxx	xx	0.xxx
Any antithrombotic agent (antiplatelet or heparin) used in first 24 hours, n (%)	xxx	xx	xxx	xx	0.xxx
Intravenous traditional Chinese medicine administered, n (%)	xxx	xx	xxx	xx	0.xxx
Intravenous steroids administered, n (%)	xxx	xx	xxx	xx	0.xxx
Hemicraniectomy performed, n (%)	xxx	xx	xxx	xx	0.xxx
Any neurosurgery performed, n (%)	xxx	xx	xxx	xx	0.xxx
Any stroke unit admission, n (%)	xxx	xx	xxx	xx	0.xxx
Any intensive care unit admission, n (%)	xxx	xx	xxx	xx	0.xxx
Any rehabilitation given, n (%)	xxx	xx	xxx	xx	0.xxx
Decision to withdrawal active care, n (%)	xxx	xx	xxx	xx	0.xxx

*Definitions for protocol violation over alteplase dose: low-dose outside 0.6-0.75 mg/kg range; standard-dose outside of 0.75mg/kg range

Table 3: Primary and secondary outcomes at 90 days, by intention to treat, except where specified

	Intensive (n=xxx) n (%)	Guideline (n=xxx) n (%)	Odds ratio (95% CI)	P-value*
mRS categories			xxx (xxx-xxx)†	0.xxx
0	xxx (xx)	xxx (xx)		
1	xxx (xx)	xxx (xx)		
2	xxx (xx)	xxx (xx)		
3	xxx (xx)	xxx (xx)		
4	xxx (xx)	xxx (xx)		
5	xxx (xx)	xxx (xx)		
6 (death before 90 days)	xxx (xx)	xxx (xx)	xxx (xxx-xxx)	0.xxx
Death or major disability (mRS score 2+3+4+5+6)				
Unadjusted	xxx (xx)	xxx (xx)	xxx (xxx-xxx)	0.xxx
Adjusted[2]	xxx (xx)	xxx (xx)	xxx (xxx-xxx)	0.xxx
Per protocol	xxx (xx)	xxx (xx)	xxx (xxx-xxx)	0.xxx
Dead or disability (mRS score 3+4+5+6)	xxx (xx)	xxx (xx)	xxx (xxx-xxx)	0.xxx
Symptomatic intracerebral haemorrhage				
SITS-MOST criteria	xxx (xx)	xxx (xx)	xxx (xxx-xxx)	0.xxx
NINDS criteria	xxx (xx)	xxx (xx)	xxx (xxx-xxx)	0.xxx
ECASS2 criteria	xxx (xx)	xxx (xx)	xxx (xxx-xxx)	0.xxx
Clinician-reported	xxx (xx)	xxx (xx)	xxx (xxx-xxx)	0.xxx
Fatal (<7 days)	xxx (xx)	xxx (xx)	xxx (xxx-xxx)	0.xxx
Any intracerebral haemorrhage	xxx (xx)	xxx (xx)	xxx (xxx-xxx)	0.xxx
Death or neurological deterioration in first 7 days	xxx (xx)	xxx (xx)	xxx (xxx-xxx)	0.xxx

*Chi-square test or, if an expected cell count is lower than 5, Fisher's exact test. If the total number of events is 0 the test is not required Chi-square test, except for†ordinal logistic regression analysis.

Table 4: Primary and secondary outcomes at 90 days, by intention to treat, by alteplase dose

	Standard BP lowering and standard-dose alteplase	Standard BP lowering and low-dose alteplase	Intensive BP lowering and standard-dose alteplase	Intensive BP lowering and low dose alteplase
		Odds ratio (95%CI) P value		Odds ratio (95%CI) P value
mRS shift				
Death or major disability (mRS score 2+3+4+5+6)				
Dead or disability (mRS score 3+4+5+6)				
Symptomatic intracerebral haemorrhage				
SITS-MOST criteria				
NINDS criteria				
ECASS2 criteria				
Clinician-reported				
Fatal (<7 days)				
Any intracerebral haemorrhage				
Death or neurological deterioration in first 7 days				

†ordinal logistic regression analysis.

Table 5: Other secondary outcomes at 90 days

	Intensive (n=xxx)		Guideline (n=xxx)		Odds ratio (95% CI)*	P-value†
	n	%	n	%		
Primary cause of death						
Direct effects of primary event	xxx	xx	xxx	xx	xxx (xx –xx)	0.xxx
Acute intracerebral haemorrhage	xxx	xx	xxx	xx	xxx (xx –xx)	0.xxx
Recurrent stroke	xxx	xx	xxx	xx	xxx (xx –xx)	0.xxx
Intracerebral haemorrhage	xxx	xx	xxx	xx		
Ischaemic stroke	xxx	xx	xxx	xx		
Undifferentiated stroke	xxx	xx	xxx	xx		
Acute MI/coronary event	xxx	xx	xxx	xx	xxx (xx –xx)	0.xxx
Other vascular	xxx	xx	xxx	xx	xxx (xx –xx)	0.xxx
Non-vascular	xxx	xx	xxx	xx	xxx (xx –xx)	0.xxx
EQ5D score						
Problems with mobility – no./total no. (%)	xxx	xx	xxx	xx	xxx (xx –xx)	0.xxx
Problems with self-care – no./total no. (%)	xxx	xx	xxx	xx	xxx (xx –xx)	0.xxx
Problems with usual activities - no./total no. (%)	xxx	xx	xxx	xx	xxx (xx –xx)	0.xxx
Problems with pain/discomfort - no./total no. (%)	xxx	xx	xxx	xx	xxx (xx –xx)	0.xxx
Problems with anxiety/depression - no./total no. (%)	xxx	xx	xxx	xx	xxx (xx –xx)	0.xxx
Overall health utility - mean±SD	xxx	xx	xxx	xx	xxx (xx –xx)	0.xxx
Living at home	xxx	xx	xxx	xx	xxx (xx –xx)	0.xxx
Duration of initial hospitalization	xxx	xx	xxx	xx	xxx (xx –xx)	0.xxx

*Chi-square test or, if an expected cell count is lower than 5, Fisher's exact test. If total number of events is 0, the test is not required

†Chi-square test or, if an expected cell count is lower than 5, Fisher's exact test.

Table 6: Serious adverse events (SAEs) during follow-up

	Intensive (n=xxx)		Guidline (n=xxx)		Odds ratio (95% CI)*	P-value†
	n	%	n	%		
All SAEs						
# of events (including deaths)	xxx	xx	xxx		NA	NA
# of subjects with any SAE	xxx	xx	xxx	xx		
Fatal SAE	xxx	xx	xxx	xx		
By category						
Neurological deterioration in the first 24 hours	xxx	xx	xxx	xx		
Neurological deterioration in the first 72 hours	xxx	xx	xxx	xx		
Death from stroke in first 7 days	xxx	xx	xxx	xx		
Death or neurological deterioration in first 7 days	xxx	xx	xxx	xx		
Symptomatic intracerebral haemorrhage	xxx	xx	xxx	xx		
Major extracranial haemorrhage	xxx	xx	xxx	xx		
Ischaemic stroke	xxx	xx	xxx	xx		
Undifferentiated stroke	xxx	xx	xxx	xx		
Acute coronary event	xxx	xx	xxx	xx		
Other vascular	xxx	xx	xxx	xx		
Non-vascular	xxx	xx	xxx	xx		
Pneumonia	xxx	xx	xxx	xx		
Sepsis	xxx	xx	xxx	xx		
Fracture	xxx	xx	xxx	xx		
Other non-vascular	xxx	xx	xxx	xx		
Angioedema	xxx	xx	xxx	xx		
Other SAE	xxx	xx	xxx	xx		

Counts correspond to the number of subjects who experienced a specific SAE with the exception of the first row. Denominators are all subjects randomized.

* if feasible and test performed

†Chi-square test or, if an expected cell count is lower than 5, Fisher's exact test. If total number of events is 0 the test is not required.

NB: Similar tables per type of SAE (fatal vs. nonfatal) may also be produced.

Table 7: Subgroup analyses – to be presented as a forest plot

	Intensive (n=xxx) n (%)	Guideline (n=xxx) n (%)	Odds ratio (95% CI)	P-value*
Age				
<65 years	xxx (xx)	xxx (xx)	xxx (xxx-xxx)	0.xxx
≥65 years	xxx (xx)	xxx (xx)	xxx (xxx-xxx)	
Sex				
Male	xxx (xx)	xxx (xx)	xxx (xxx-xxx)	0.xxx
Female	xxx (xx)	xxx (xx)	xxx (xxx-xxx)	
Ethnicity				
Asian	xxx (xx)	xxx (xx)	xxx (xxx-xxx)	0.xxx
Non-Asian	xxx (xx)	xxx (xx)	xxx (xxx-xxx)	
Time to randomisation				
<3 hours	xxx (xx)	xxx (xx)	xxx (xxx-xxx)	0.xxx
≥3 hours	xxx (xx)	xxx (xx)	xxx (xxx-xxx)	
Baseline systolic BP				
Below overall mean	xxx (xx)	xxx (xx)	xxx (xxx-xxx)	0.xxx
Above overall mean	xxx (xx)	xxx (xx)	xxx (xxx-xxx)	
Baseline NIHSS score				
Below overall median	xxx (xx)	xxx (xx)	xxx (xxx-xxx)	0.xxx
Above overall median	xxx (xx)	xxx (xx)	xxx (xxx-xxx)	
Final diagnosis of AIS				
Large artery atheroma occlusion	xxx (xx)	xxx (xx)	xxx (xxx-xxx)	0.xxx
Small vessel disease	xxx (xx)	xxx (xx)	xxx (xxx-xxx)	
Cardio-embolic	xxx (xx)	xxx (xx)	xxx (xxx-xxx)	
Other definite or uncertain pathology	xxx (xx)	xxx (xx)	xxx (xxx-xxx)	
Pre-morbid use of aspirin				
Yes	xxx (xx)	xxx (xx)	xxx (xxx-xxx)	0.xxx
No	xxx (xx)	xxx (xx)	xxx (xxx-xxx)	
History of hypertension				
Yes	xxx (xx)	xxx (xx)	xxx (xxx-xxx)	0.xxx
No	xxx (xx)	xxx (xx)	xxx (xxx-xxx)	
Dose of alteplase				
Standard	xxx (xx)	xxx (xx)	xxx (xxx-xxx)	0.xxx
Low	xxx (xx)	xxx (xx)	xxx (xxx-xxx)	

Figure 1: Flow diagram of ENCHANTED blood pressure control arm based on CONSORT 2010

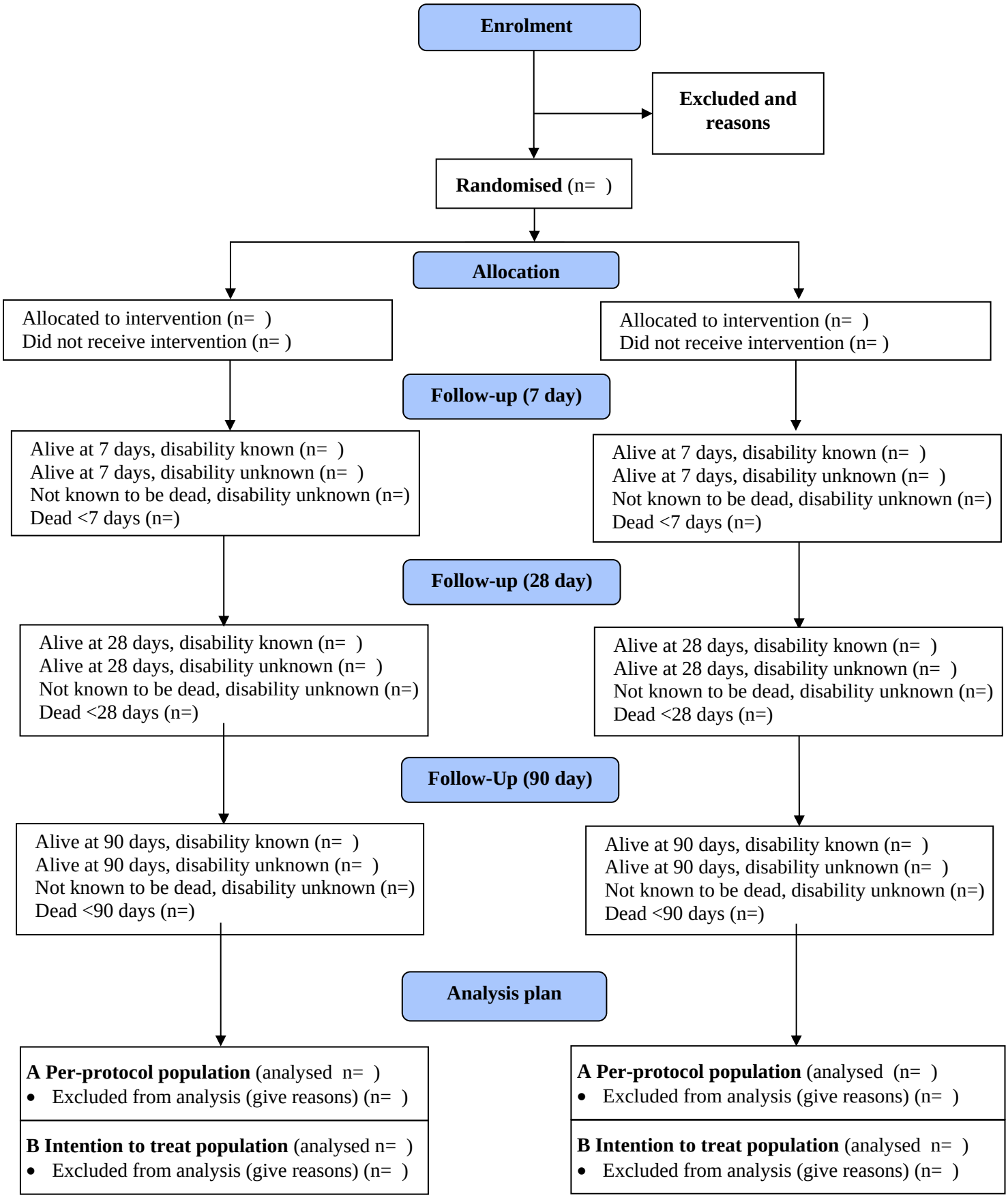
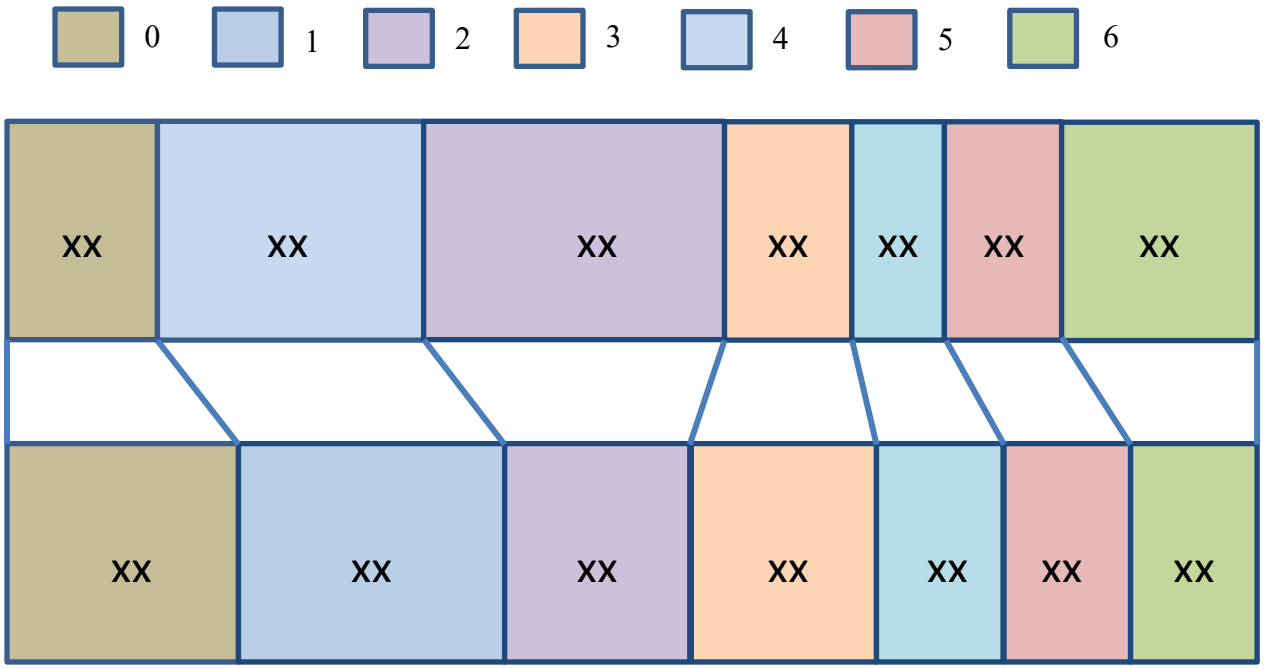


Figure 2. Levels of systolic blood pressure by treatment group

Figure 3: Modified Rankin score (mRS) outcome at 90 days by treatment group

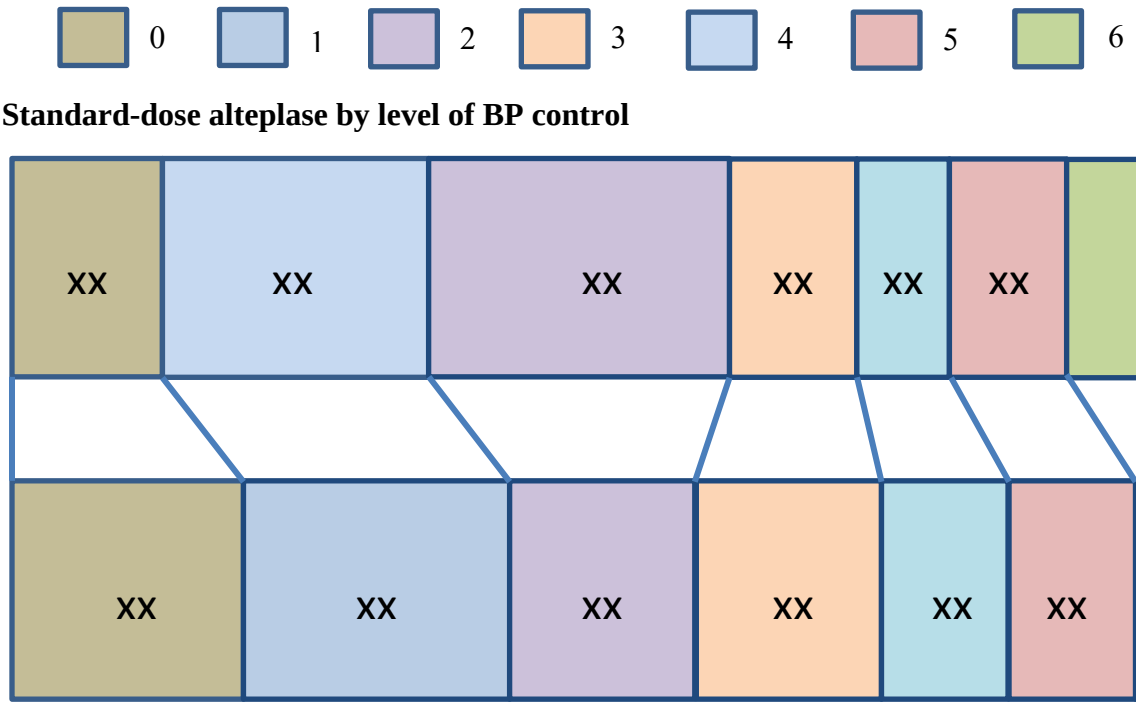


Patients_(%)

xx refer to percentage values in each level of mRS

Unadjusted common odds ratio for improvement of 1 point on the mRS is XX (95% CI X.XX to X.XX).

Figure 4: Modified Rankin score (mRS) outcome at 90 days by treatment group, according to alteplase dose



xx refer to percentage values in each level of mRS

Adjusted common odds ratio for improvement of 1 point on the mRS is XX (95% CI X.XX to X.XX). P value for interaction included.

Appendix 3

Additional tables

Table 1: Compliance with trial treatment protocol

	Intensive (n=xxx) N (%)*	Guidline (n=xxx) N (%)*
Randomisation violations		
Age <18 years	xxx (xx)	xxx (xx)
Acute stroke syndrome not ischaemic stroke	xxx (xx)	xxx (xx)
Dependent pre-stroke	xxx (xx)	xxx (xx)
Significant comorbid condition	xxx (xx)	xxx (xx)
Systolic BP >185 mmHg prior to alteplase	xxx (xx)	xxx (xx)
Systolic BP <150 mmHg prior to randomisation	xxx (xx)	xxx (xx)
Other	xxx (xx)	xxx (xx)
Treatment compliance		
Alteplase not given	xxx (xx)	xxx (xx)
BP lowering treatment protocol not followed	xxx (xx)	xxx (xx)
Outcome assessment		
In-person or telephone assessment of 90 day outcome	xxx (xx)	xxx (xx)
Assessor predicted treatment allocation	xxx (xx)	xxx (xx)

*denominator will vary for violations and compliance/outcomes

Table 2: Other categorisation of baseline characteristics

	Intensive group (n=xxx)	Guideline group (n=xxx)
Age, years		
18-40	xxx (xx)	xxx (xx)
40-50	xxx (xx)	xxx (xx)
50-60	xxx (xx)	xxx (xx)
60-70	xxx (xx)	xxx (xx)
70-80	xxx (xx)	xxx (xx)
80-90	xxx (xx)	xxx (xx)
>90	xxx (xx)	xxx (xx)
≥80	xxx (xx)	xxx (xx)
Region of recruitment		
UK/Europe/Australia	xxx (xx)	xxx (xx)
China	xxx (xx)	xxx (xx)
Other Asian	xxx (xx)	xxx (xx)
South America	xxx (xx)	xxx (xx)
NIHSS score		
0-5	xxx (xx)	xxx (xx)
6-10	xxx (xx)	xxx (xx)
11-15	xxx (xx)	xxx (xx)
16-20	xxx (xx)	xxx (xx)
21-35	xxx (xx)	xxx(xx)
Time to randomisation, hr		
0-1	xxx (xx)	xxx (xx)
1-2	xxx (xx)	xxx (xx)
2-3	xxx (xx)	xxx (xx)
3-4	xxx (xx)	xxx (xx)
>4	xxx (xx)	xxx(xx)
Medical history		
Previous stroke	xxx (xx)	xxx (xx)
Documented extra-cranial vascular disease	xxx (xx)	xxx (xx)
Documented intra-cranial vascular disease	xxx (xx)	xxx (xx)

Table 3: BP lowering treatment

	Standard BP control (n=xxxx)	Early intensive BP lowering (n=xxxx)
BP lowering in the first 24 hours after randomisation		
Highest BP mmHg, mean (SD)	xxx (xx)	xxx (xx)
Lowest BP mmHg, mean (SD)	xxx (xx)	xxx (xx)
Intravenous agents used, n (%)		
Alpha-adrenoreceptor antagonists *(e.g urapidil)*	xxx (xx)	xxx (xx)
Alpha and Beta Blocking agents *(e.g labetalol)*	xxx (xx)	xxx (xx)
Beta Blocking agents*(e.g. metoprolol)*	xxx (xx)	xxx (xx)
Calcium Channel Blockers *(e.g nicardipine, nimodipine)*	xxx (xx)	xxx (xx)
Clonidine	xxx (xx)	xxx (xx)
Diuretics *(e.g frusemide)*	xxx (xx)	xxx (xx)
Glycerol trinitrate	xxx (xx)	xxx (xx)
Hydrazaline	xxx (xx)	xxx (xx)
Nitroprusside	xxx (xx)	xxx (xx)
Phentolamine	xxx (xx)	xxx (xx)
Other	xxx (xx)	xxx (xx)
Topical nitrates	xxx (xx)	xxx (xx)
Oral agents used, n (%)		
Angiotension converting enzyme inhibitor or Angiotension receptor blocker	xxx (xx)	xxx (xx)
Calcium channel blocker	xxx (xx)	xxx (xx)
Diuretic	xxx (xx)	xxx (xx)
Beta blocker	xxx (xx)	xxx (xx)
Other	xxx (xx)	xxx (xx)
BP lowering treatment in days 2-7		
Any BP lowering treatment, n (%)	xxx (xx)	xxx (xx)
Any intravenous BP lowering treatment, n (%)	xxx (xx)	xxx (xx)
Number of intravenous agents, n (%)		
1	xxx (xx)	xxx (xx)
2	xxx (xx)	xxx (xx)
≥3	xxx (xx)	xxx (xx)
BP lowering treatment at day 90		
Any BP lowering treatment, n (%)	xxx (xx)	xxx (xx)
Number of agents, n (%)		
1	xxx (xx)	xxx (xx)
2	xxx (xx)	xxx (xx)
≥3	xxx (xx)	xxx (xx)

Table 4: PP population - baseline characteristics

	Intensive group (n=xxx)	Guidline group (n=xxx)
Time from stroke onset to randomisation (hrs:mins), mean (SD) and median (iqi)	xxx (xx)	xxx (xx)
Male, n (%)	xxx (xx)	xxx (xx)
Age (years), mean (SD)	xxx (xx)	xxx (xx)
median (iqi)	xxx (xx)	xxx (xx)
≥80, n (%)	xxx (xx)	xxx (xx)
Ethnicity		
Asian, n (%)	xxx (xx)	xxx (xx)
Other, n (%)	xxx (xx)	xxx (xx)
Clinical features		
Systolic BP (mmHg), mean (SD)	xxx (xx)	xxx (xx)
Diastolic BP (mmHg), mean (SD)	xxx (xx)	xxx (xx)
Heart rate (beats per minute), mean (SD)	xxx (xx)	xxx (xx)
NIHSS score		
Median (iqi)	xxx (xx)	xxx (xx)
≥14 (n, %)	xxx (xx)	xxx (xx)
GCS score		
Median (iqi)	xxx (xx)	xxx (xx)
Severe (3-8), n (%)	xxx (xx)	xxx (xx)
Medical history		
Hypertension, n (%)	xxx (xx)	xxx (xx)
Currently treated hypertension, n (%)	xxx (xx)	xxx (xx)
Previous stroke (ischaemic, haemorrhagic or uncertain), n (%)	xxx (xx)	xxx (xx)
Coronary artery disease, n (%)	xxx (xx)	xxx (xx)
Other heart disease (valvular or other), n (%)	xxx (xx)	xxx (xx)
Evidence of atrial fibrillation, n (%)		
Definite history of atrial fibrillation n (%)	xxx (xx)	xxx (xx)
Atrial fibrillation confirmed on ECG, n (%)	xxx (xx)	xxx (xx)
Diabetes mellitus, n (%)	xxx (xx)	xxx (xx)
Hypercholesterolaemia, n (%)	xxx (xx)	xxx (xx)
Current smoker, n (%)	xxx (xx)	xxx (xx)
Pre-stroke function (mRS), n (%)		
0 no symptoms	xxx (xx)	xxx (xx)
1 no significant disability	xxx (xx)	xxx (xx)
Medications at time of admission		
Antihypertensive agent(s), n (%)	xxx (xx)	xxx (xx)
Warfarin anticoagulation, n (%)	xxx (xx)	xxx (xx)
Aspirin or other antiplatelet agent, n (%)	xxx (xx)	xxx (xx)
Statin or other lipid lowering agent, n (%)	xxx (xx)	xxx (xx)
Brain imaging features		

CT scan used, n (%)	xxx (xx)	xxx (xx)
MRI scan used, n (%)	xxx (xx)	xxx (xx)
Visible early ischaemic changes, n (%)	xxx (xx)	xxx (xx)
Visible cerebral infarction, n (%)	xxx (xx)	xxx (xx)
Visible cerebral infarction with mass effect, n (%)	xxx (xx)	xxx (xx)
CT or MR angiogram show proximal occlusion, n (%)	xxx (xx)	xxx (xx)
Final diagnosis at time of hospital separation		
Non-stroke, n (%)		
migraine	xxx (xx)	xxx (xx)
seizure	xxx (xx)	xxx (xx)
functional weakness	xxx (xx)	xxx (xx)
syncope	xxx (xx)	xxx (xx)
other	xxx (xx)	xxx (xx)
Presumed stroke pathology, n (%)		
Large artery occlusion due to significant atheroma	xxx (xx)	xxx (xx)
Small vessel or perforating vessel lacunar disease	xxx (xx)	xxx (xx)
Cardio-emboli	xxx (xx)	xxx (xx)
Other or uncertain aetiology		

Appendix 4

Proposed content and timing of primary and subsequent publications

N	2019
1	Main results paper: differential treatment effects of BP control on primary and secondary efficacy and safety outcomes, and according to pre-specified subgroups
2	Further subgroup analysis: relation of treatment effects by dose interaction, ethnicity, and age
3	Further subgroup analysis: differential treatment effects by proximal clot occlusion of CT or MRI angiography
4	Further subgroup analysis: differential treatment effects by baseline neurological severity
5	Differential treatment effects according to use of endovascular clot retrieval
	2020 and subsequent years
6	Differential treatment effects of BP control on degree of cerebral ischaemic lesion and brain frailty markers identified on brain imaging
7	Predictors of intracerebral haemorrhage
8	Clinical and imaging predictors of poor outcome
9	Health economic analysis: estimating cost-effectiveness by BP control
10	Determinants of HRQoL and influence of age, sex, ethnicity and level of disability
11	Quality of stroke service parameters and outcome
12	Patterns of recovery according to mRS scores over 7, 28 and 90 days follow-up
13	Structural imaging descriptive analyses and correlation of perfusion imaging with plain CT
14	Clinical-radiological correlations of baseline imaging and clinical and pathological classifications
15	Inclusion of data in systematic reviews/meta-analyses including the Blood pressure in Acute Stroke Collaboration (BASC), Cochrane Stroke Group database of thrombolytic dose, and of brain imaging determinants of AIS outcome (J Wardlaw, University of Edinburgh)

Appendix 5: Statement of contribution of the authors

CA and TR wrote the first draft and led all revisions of the SAP. MW, RIL, XC and XW conducted revisions of the SAP. HA and JC participated in critical reviews of the SAP. The final version of the SAP was approved by the ENCHANTED Steering Committee on 10 August 2018. The SAP was prepared without knowledge of the unblinded data. The unblinded study statisticians prepared tabulations of the baseline characteristic as grouped data for reports during the course of the study, which were used to inform the authors in selection of cut-points to define subgroups and aspects of the overall analysis plan. The SAP was prepared independent of the key funding agency for the trial, the Australian National Health and Medical Research Council (NHMRC).