Enchanted

Enhanced Control of Hypertension and Thrombolysis Stroke Study

The ENCHANTED is an international randomised controlled trial to establish the effects of low–dose rtPA and the effects of early intensive blood pressure lowering in patients with acute ischaemic stroke

STUDY PROTOCOL

(Version 5.0– 16 Feb 2017)

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INVESTIGATOR AGREEMENT

I have read this protocol and agree that it contains all the necessary details for carrying out the study. I will conduct the study as outlined herein and will complete the study within the time designated.

I will provide copies of the protocol and all pertinent information to all individuals responsible to me who assist in the conduct of the study. I will discuss this material with them to ensure that they are fully informed regarding the study intervention and the conduct of the study.

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Investigator's Signature *Date (Day / Month / Year)*

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List of abbreviations and definition of terms

ACE-I	Angiotensin Converting Enzyme Inhibitor
AE/SAE	Adverse Event / Serious AE
AHA	American Heart Association
AIS	Acute Ischaemic Stroke
BP	Blood Pressure
CI	Confidence Interval
CRF/eCRF	Case report form / Electronic CRF
CT	Computerised tomography
CV	Curriculum Vitae
DSMB	Data Safety Monitoring Board
EC	Executive Committee
ECG	Electrocardiogram
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GCS	Glasgow Coma Scale
GI	The George Institute for Global Health
HR	Heart Rate
HREC	Human Research Ethics Committee
HRQoL	Health Related Quality of Life
IAC	Imaging Adjudication Committee
ICC	International Coordinating Centre
ICH	Intracerebral Haemorrhage
ICH-GCP	International Conference on Harmonisation for Good Clinical Practice
ICMJE	International Committee of Medical Journal Editors
IRB	Institutional Review Board
ITT	Intention to Treat
IVRS	Interactive Voice Randomisation System
mins	Minutes
MRC	Medical Review Committee
MRI	Magnetic Resonance Imaging
mRS	Modified Rankin Scale
NB	Note
NHMRC	National Health and Medical Research Council of Australia
NIHSS	National Institute of Health Stroke Scale
NINDS	National Institute of Neurological Disorders and Stroke

OC	Operations Committee
OR	Odds Ratio
PI	Principal Investigator
RCCs	Regional Coordinating Centres
rtPA	Recombinant tissue plasminogen activator
SAP	Statistical Analysis Plan
SC	Steering committee
SD	Standard Deviation
sICH	Symptomatic intracerebral haemorrhage
TCD	Trans-cranial Doppler
TOAST	Trial of Org in Acute Stroke Treatment
WHO	World Health Organisation

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SUMMARY PROTOCOL

ENCHANTED is an independent, investigator initiated, international collaborative, quasi-factorial randomised controlled trial involving a package of 2 linked comparative treatment arms, which aims to address 4 key questions in patients eligible for thrombolysis in the hyperacute phase of ischaemic stroke. (1) Does low-dose (0.6 mg/kg) intravenous (i.v.) recombinant tissue plasminogen activator (rtPA) provide *equivalent* benefits compared to standard-dose (0.9 mg/kg) rtPA? (2) Does intensive blood pressure (BP) lowering (130-140 mmHg systolic target) *improve* outcomes compared to the current guideline recommended level of BP control (<180 mmHg systolic target)? (3) Does low-dose (0.6 mg/kg) i.v. rtPA *reduce* the risk of symptomatic intracerebral haemorrhage (sICH)? (4) Does the addition of intensive BP lowering to thrombolysis with rtPA *reduce* the risk of any ICH?

Reason for this Protocol amendment from version 4.0 to version 5.0: The rtPA dose arm of the study addressing questions (1) and (3) concluded with a publication of the results in May 2016. The BP intensity arm of the study is ongoing and the protocol has been modified to reflect changes.

Background and rationale Modern therapy for acute ischaemic stroke (AIS) is based on the premise that early vessel re-canalisation and reperfusion are essential for the preservation of brain function and promotion of satisfactory outcome. RtPA is the only approved treatment of AIS, licensed on the basis of the NINDS trial, where an i.v. dose of 0.9 mg/kg within 3 hours of symptom onset was shown to improve clinical outcomes with an acceptable risk of sICH, although the time criteria for use has recently been extended to 4.5 hours on the basis of subsequent randomised evidence. However, 0.6 mg/kg is the standard approved dose of rtPA in Japan, where non-randomised studies have shown comparable clinical outcomes and a reduced risk of sICH compared to expected rates for the standard dose. Thus, low dose rtPA (i.e. which generally requires use of a single 50mg vial of Actilyse ®Boehringer Ingelheim) has become an attractive 'cheaper' treatment option for patients who cannot afford the full dose (i.e. 2 vials) in much of Asia. In the absence of randomised evidence, however, there is ongoing uncertainty as to whether low-dose rtPA is truly equivalent in efficacy, or even safer, to the standard dose, not just in Asians but in other population groups around the world. The optimal management of BP in AIS remains controversial. Although BP levels are commonly elevated, the effects of BP lowering in the hyperacute phase of stroke remain unknown. Guidelines for BP control in AIS are consistent in contraindicating use of rtPA in patients with systolic BP >185 mmHg and diastolic BP >110 mmHg, but recent data suggests that lower BP levels may achieve better outcomes. The most compelling data are from large-scale prospective registry studies, such as SITS-MOST, where elevated baseline systolic BP are associated with a worse outcome and elevated risk of sICH post-rtPA. None of the recently completed (and ongoing) trials in the area have been specifically designed to address the role of rapid intensive BP lowering within the first few hours of stroke onset, and in particular, as to whether such treatment improves outcomes after rtPA. The second main phase INTERACT2 study showed that rapid BP lowering (140 mmHg systolic target) is feasible, safe and potential efficacious in improving functional recovery in patients with acute intracerebral haemorrhage.

Hypotheses In patients with AIS eligible for thrombolysis with rtPA according to local guidelines and otherwise able to receive best usual medical care, the ***primary aims*** are to determine: **[A]** whether compared to the standard dose, low-dose rtPA is at least as effective (*'not inferior'*) on death or disability (i.e. null hypothesis is that low-dose is inferior to standard dose rtPA); **[B]** whether compared with current guideline recommended criteria for BP management, early intensive BP lowering is *superior* at improving functional outcome according to an ordinal comparison of the full range of scores on the modified Rankin scale (mRS) between groups (i.e. null hypothesis is that there is no difference in the intensities of BP control on this outcome). The ***key secondary aims*** are to determine **[C]** whether compared with standard dose rtPA, low-dose rtPA reduces the risk of sICH; **[D]** whether compared with standard guideline-based BP management, early intensive BP lowering after rtPA reduces the risk of any ICH (i.e. 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*** are to define the effects of the treatments on symptomatic and any ICH; good outcome (mRS 0-1), death or major disability (mRS 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.

Inclusion/exclusion criteria Patients with clinical diagnosis of AIS confirmed by brain imaging within 4.5 hours of onset who fulfil local criteria for use of i.v. rtPA are potentially eligible if they have a sustained systolic BP level ≤185 mmHg (i.e. the guideline recommended level of eligibility for rtPA; patients with higher BP levels at presentation can still be included provided the BP is reduced to the entry level prior to commencement of the treatment). The attending clinician is required to consider their level of clinical uncertainty over the balance of potential benefits and risks pertaining to use of rtPA and the level of BP control in each particular patient: *arm **[A]** of low- vs standard-dose rtPA has now closed*; and *arm **[B]** of intensive vs guideline recommended BP control*: (a) sustained elevated systolic BP level (i.e ≥150 and ≤185 mmHg over 6 hours from the onset of symptoms; the upper level guideline recommended for the use of rtPA); (b) able to receive either intensive BP lowering or conservative BP management [no definite indication/contraindication to 'intensive' BP lowering (i.e. target 130-140 mmHg systolic)]. *Exclusion criteria*: (a) unlikely to potentially benefit from the therapy (e.g. advanced dementia) or a very high likelihood of death within 24 hours of stroke onset; (b) other medical illness that interferes with outcome assessments and follow-up (e.g. known significant pre-stroke disability (mRS scores 2-5), advance cancer and renal failure); (c) specific contraindications to rtPA (Actilyse) or any of the BP agents to be used; (d) participation in another clinical trial involving evaluation of pharmacological agents; and (e) need for following concomitant medication, including phosphodiesterase inhibitors and monoamine oxidase inhibitors.

Randomised interventions Randomisation is via a central internet-based system developed by The George Institute, Sydney, Australia, either direct or via a specially developed IVRS (only in China), stratified by site, time from onset (<3 vs ≥3 hours) and NIHSS (<10 vs ≥10) to ensure balance in key prognostic factors. All patients must be eligible for i.v. rtPA and those with elevated BP are eligible for arm **[B]**. Recruitment of patients into arm A completed in August 2015. Arm **[B]** involves intensive BP lowering to a target systolic BP range 130-140 mmHg within 60 minutes of randomisation into the BP arm and to maintain this level for at least 72 hours (or until hospital discharge or death if this should occur earlier) or guideline-based BP lowering to a target systolic BP of <180 mmHg post-rtPA. Standardised locally approved i.v. BP lowering agents are to be used.

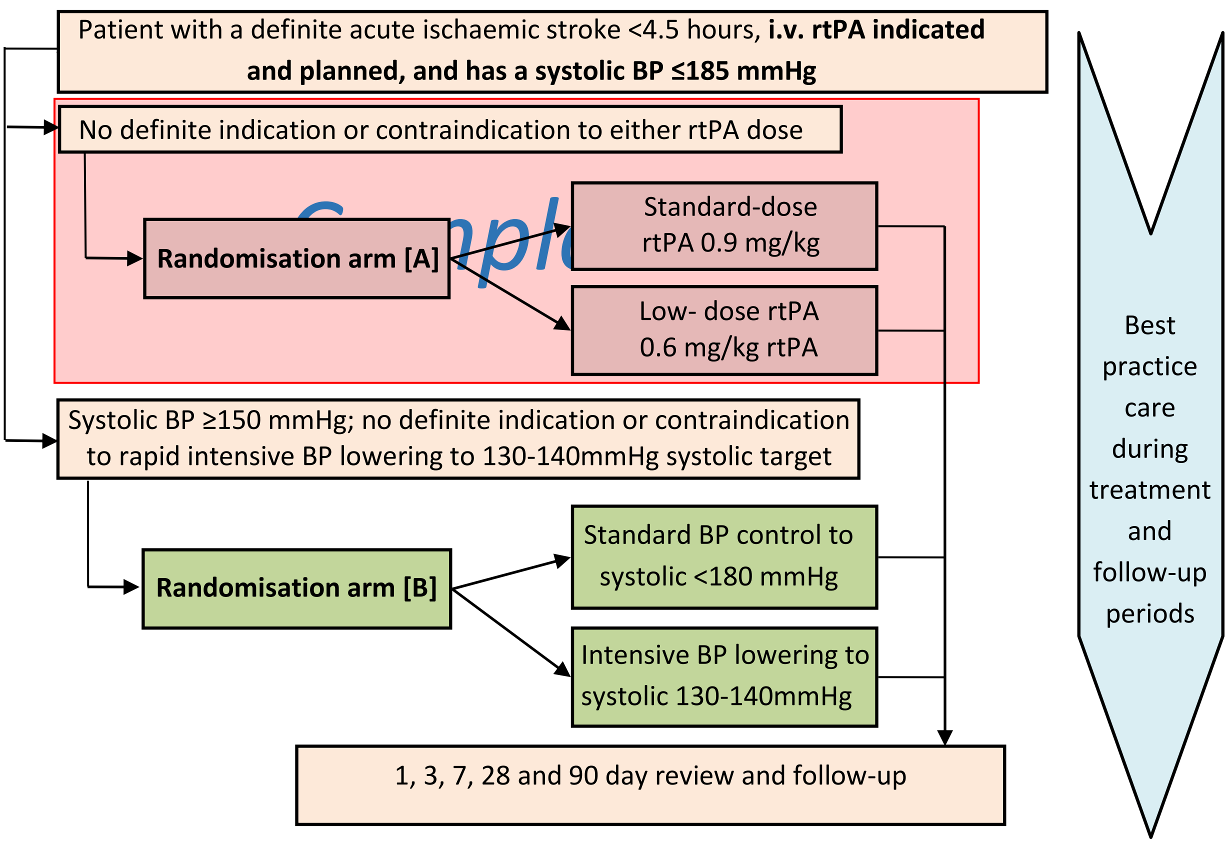
Data collection and follow-up Registration, baseline, and randomisation to be achieved in 30 minutes. Patients followed daily for 1 week and at 28 and 90 days unless death occurs earlier. Follow-up data are collected at 24 and 72 hours, and 7 (or at time of death or hospital discharge if sooner), 28 and 90 days. The 28 and 90 day evaluation will be conducted in-person or by telephone by a trained local staff member who is blind to treatment allocation. Brain imaging (CT scans or MRI) will be conducted according to standardised techniques at baseline, within the next 24 hours, and at a later stage in survivors who deteriorate or for other reason. Trial management is by an established internet-based system.

Outcomes Primary: in Arm A, the efficacy of the treatment was evaluated on the combined endpoint of death and disability (mRSscore 2-6) at the end of follow-up. In Arm B, efficacy of the treatment will be evaluated on an ordinal comparison of the full range of scores on the mRS at the end of follow-up. In Arm B, the secondary outcomes involve determining the effects of treatments on any ICH, sICH, good outcome (mRS 0-1), death or major disability (mRS 3-6), separately on death and major disability (mRS 3-5), early neurological deterioration, HRQoL, and health service use for calculation of resources and costs.

Statistical considerations A sample size of 3300 (1650 per group) estimated for arm **[A]** (i.e. rtPA dose) estimated to provide (i) >90% power to detect non-inferiority (relative margin 14% [i.e. relative risk 1.14], absolute margin rate 6.5%) of low-dose rtPA on the primary outcome (one-sided $\alpha = 0.025$) and (ii) ≥80% power to detect plausible 40% reductions in risks of sICH with low-dose rtPA (2-sided $\alpha = 0.05$) with 5% drop-out was achieved. . Arm **[A]** completed recruitment in August 2015 with 3310 patients randomised. A sample size of 2100 (1050 per group) for arm **[B]** (i.e. BP lowering intensities) will provide ≥80% power to detect superiority of intensive BP lowering on the primary outcome and any ICH (2-sided $\alpha = 0.10$) with 5% drop-out. Given overlap of 939 patients in the combined arms **[A]** and **[B]**, an expected total of 4500 patients will participate in the study.

Quality assurance and bias control The study will be conducted at sites with established acute stroke units and thrombolysis programs. Regionally-based clinical research monitors will perform online, on-site data verification; and monitor conduct of the study, initially after the first few patients are randomised at a site and then at least once annually, according to patient recruitment numbers, whilst participating in the trial. As ENCHANTED is an open trial of differing management strategies in a critical illness, monitoring serves to confirm that investigators are adhering to the protocol and GCP Guidelines, and the accuracy of data. Monitoring by trained staff will confirm: (i) demographic and consent details of randomised patients; (ii) details of all SAEs against source documents; (iii) collect/correct outstanding/missing data; and (iv) check selected variables against source documents in a 10% random selection of patients.

Study organization A *Steering Committee (SC)* comprises country academic leaders and includes an *Executive sub-Committee* who are the grant holders from the National Health and Medical Research Council (NHMRC) of Australia, an *Operational Committee* based at the *International Coordinating Centre (ICC)* is in charge of the central coordination of the study from The George Institute, Sydney*, Regional Coordinating Centres (RCCs),* an independent *Data Safety Monitoring Board (DSMB)*, an *Imaging Adjudication Committee (IAC),* a *Medical Review Committee,* and an *Advisory Committee* of international experts. A total of 100+ sites are required, most in Asia (approximately 60 sites) and Australia/New Zealand, Europe (approximately 40 sites), and South America (approximately 30 sites), to achieve the sample of 4500 patients (50% from Asia) over 6 years (av. 6 patients per site per year). Sites will be administratively tied through a structure designed to enhance effective communication and collaboration as well as monitor and maintain operations through adherence to a common protocol. Central coordination is from The George Institute, Sydney. The inclusion of focused substudies, for which separate funding will be sought, will advance the understanding of pathophysiological mechanisms of acute ischaemic stroke, the interpretation of the results, and inform clinical care and future studies. Sites will receive AUD $400 per patient to cover administrative and other direct costs. As rtPA is an expensive agent, payments will also be provided to selected sites to subsidise the cost of rtPA.



INTRODUCTION

Ischaemic stroke caused by acute occlusion of an artery leading to immediate reduction in blood flow within the corresponding cerebrovascular territory, causes 9% of all deaths around the world, and is associated with a very high health-care and socioeconomic costs.

Early spontaneous re-canalisation may occur from the endogenous release of rtPA, a serine protease of the fibrinolytic system. However, for most patients, this natural physiological function is inadequate to avoid the outcome of infarcted cerebral tissue from the occluded vessel. rtPA is the only approved treatment of acute ischaemic stroke (AIS) despite increased risk of symptomatic intracerebral haemorrhage (sICH). Recent studies suggest that low-dose rtPA is an effective treatment and may have a reduced risk of sICH but there is lack of reliable randomised evidence to support it.

BP levels are commonly elevated (systolic >140 mmHg) after the onset of the stroke. The effects of BP lowering treatment in the acute phase of stroke remain unknown. As a consequence, there are wide ranging guideline recommendations for the management of elevated BP in these group of patients. There is increasing evidence to suggest that early intensive BP lowering therapy in patients with acute stroke therapy may benefit, but a large-scale clinical trial is required to reliably determine the overall balance of risks and benefits of such intervention.

ENCHANTED has been designed to resolve these areas of major persisting clinical uncertainty and provide definitive evidence on the effectiveness of a potentially widely applicable treatment policy in a large and increasing patient population.

Novel features of the study include: (a) clinician flexibility in the randomisation of patients; (b) ability of analyses to examine the individual and combined effects of the treatments; (c) use of an established research infrastructure and global clinical network for 2 large-scale academic stroke trials - the third International Stroke Trial (IST-3)[1] of i.v. rtPA within 6 hours of acute ischaemic stroke, and the Intensive Blood Pressure Reduction in Acute Cerebral Haemorrhage Trial (INTERACT2) of rapid intensive (140 mmHg systolic target) versus guideline-recommended level (180 mmHg systolic target) of BP lowering within 6 hours of spontaneous intracerebral haemorrhage (ICH)[2] - provides efficacy gains and assurance over feasibility, recruitment and completion; (d) use of broad inclusion criteria and conduct of the study across different health care settings will support the generalisability of results; and (e) a comparative effectiveness design with restricted availability of reduced cost rtPA offers ‘active’ equitable treatment and ability to improve stroke care at participating sites in developing countries.

BACKGROUND

1. EPIDEMIOLOGY

Stroke is the 4th leading cause of global disease burden, resulting in an estimated 16 million first-ever events, 62 million survivors, 51 million disability-adjusted life years (DALYs) lost, and 5.7 million deaths (87% in low-middle income countries) in 2005.[3] However, because of the ageing population, the burden will increase greatly during the next 20 years, with developing countries more affected. In western societies, about 80% of strokes are caused by focal neurological ischaemia, and the remaining 20 % are caused by haemorrhages. Thirty-day case fatality rates for AIS in western societies range between 10 and 17%. Mortality in the first month after stroke has been reported to range from 2.5% in patients with lacunar infarct to 78% in patients with space-occupying hemispheric infarction.

2. PATHOPHYSIOLOGY

Ischaemic stroke is caused by acute occlusion of an artery leading to immediate reduction in blood flow within the corresponding cerebrovascular territory. The size and site of the occlusion, and the efficiency of compensatory collateral blood flow, determine the extent of impaired blood flow and resulting neurological symptoms from 'at risk' ('ischaemic') and/or dead ('infarcted') brain. Early spontaneous re-canalisation may occur from the endogenous release of tPA, a serine protease of the fibrinolytic system which converts the zymogen plasminogen into the active protease plasmin, leading to cleavage of fibrin and the dissolving of newly formed thrombin 'clot'. However, for most patients, and particularly in those with large occlusions, this natural physiological function is inadequate to avoid the outcome of infarcted cerebral tissue from the occluded vessel.

3. ACUTE MANAGEMENT

The immediate goals of acute ischaemic stroke, as other forms of stroke, include firstly to minimise brain injury; and secondly to prevent future neurological damage. Strong evidence has shown that treatment of patients in stroke units reduces mortality, dependency and the need for institutional care.

The general physical examination continues from the original assessment of the ABCs and should include pulse oximetry and body temperature. Deficit should be assessed by a brief but thorough neurological examination, several scales has been developed to quantify the severity of the neurological deficit. Standardised examinations help to ensure that major components of a neurological examination are performed in timely fashion. These scores not only help to quantify the degree of neurological damage but also identify the possible location of the vessel occlusion, provide early prognosis, and help to identify patient eligibility for various interventions and the potential for complications. The National Institutes of Health Stroke Scale (NIHSS) is most often used. In addition a further attempt to identify the mechanism that leads to vessel occlusion based on Trial of Org in Acute Stroke Treatment (TOAST) criteria (cardio-embolic, artery-to-artery embolism, or in-situ small vessel 'lacunar' disease) is recommended as information should influence both acute treatment and secondary prevention strategies Table 1**.**

Table 1 Classification of subtypes of acute ischaemic stroke

TOAST* (Trial of Org 10 172 in Acute Stroke Treatment) criteria
Large-artery atherosclerosis (embolus or thrombosis)*
Cardioembolism (high-risk or medium-risk)*
Small-vessel occlusion (lacune)*
Stroke of other determined cause*
Stroke of undetermined cause
Two or more causes identifi ed
Negative evaluation
Incomplete evaluation
*Possible or probable depending on results of ancillary studies.

Cardiac examination, cardiac enzymes test and a 12 lead ECG should be performed in all stroke patients as cardiac abnormalities are prevalent in this group of patients. In addition routine blood test should be performed in patient with suspected AIS to identify systemic conditions that may mimic or cause stroke or that may influence therapeutic options. These tests include blood glucose, electrolytes, complete blood account with platelet account, prothrombin time, activated partial thromboplastin time, international normalized ratio and renal function test. *Thrombolytic therapy should not be delayed while waiting for results unless a bleeding abnormality or thrombocytopenia is suspected, the patient has been taking warfarin, or anticoagulation use is uncertain*.

Additional tests may be performed as indicated by the patient's history, symptoms, physical findings, or co-morbidities. A toxicology screen, blood alcohol level, arterial blood gas, and pregnancy test should be obtained if the physician is uncertain about the patient's history or as suggested by findings on examination.

Brain imaging remains a required component of the emergency assessment of patients with stroke. Both computed tomography (CT) and magnetic resonance imaging (MRI) are options for imaging of the brain. CT may suffice as compared with MRI, as it is more widely available, faster, less susceptive to motion artifacts, and cheaper. On the other hand, MRI has a much higher sensitivity than CT for acute ischaemic changes especially in the posterior fossa. Imaging of the intracranial and extracranial vasculature in emergency assessment of patients with suspected stroke is useful in institutions providing endovascular recanalisation therapies.

Restoration of blood flow using thrombolytic therapy is the most effective treatment for salving ischaemic brain tissue that is not already undergoing infarction. Therefore, once an ischaemic stroke is confirmed by history, clinical examination and neuroimaging (CT brain or MRI), rapid determination of patients eligibility for thrombolysis is required as the benefit of i.v. thrombolysis decreases rapidly and continuously over time. Current guidelines recommend 0.9 mg/kg rtPA (10% bolus, 1 hour infusion, 90mg max. dose) within 4.5 hours of the onset of symptoms in patients eligible for thrombolysis, based on results of the pivotal National Institute of Neurological Disorders and Stroke (NINDS) trial.[4] Clot-retrieval devices, used either alone or as an adjuvant to thrombolysis, have recently been shown to be effective in patients with AIS due to occlusion of proximal cerebral vessels.[5] But the use of these devices is limited to comprehensive stroke centres that have the resources and physician expertise to perform these procedures safely. The administration *of anticoagulants or antiplatelet agents is currently contraindicated during the first 24 hours after treatment with rtPA* based on the protocol used in the NINDS trial. The experience with adjunctive anticoagulation is limited; neither safety nor effectiveness has been established.

Aspirin is the only oral antiplatelet agent that has been evaluated for the treatment of AIS with a small but significant decline in mortality and morbidity when started within 48 hours of onset of stroke. However, patients with prior use of aspirin who receive thrombolysis may have an increased mortality in AIS. Aspirin should not be considered a substitute for other acute intervention for the treatment of stroke, including the intravenous administration of rtPA.

Guidelines recommendations regarding BP control in patients with AIS are based in consensus, since there are no data supporting any specific antihypertensive regimen. Given concerns about adverse effects of the short-term lowering BP on cerebral perfusion, current guidelines recommended withholding antihypertensive therapy during the acute phase of stroke unless the BP exceeds 220/120 mmHg in patient who are not candidates for rtPA (see Table 2).

In patients receiving thrombolytic therapy, BP levels of ≤185/110 should be achieved prior receiving rtPA therapy and intravenous antihypertensive therapy is recommended to maintain the BP target below 180/105 mmHg after treatment with rtPA (see Table 3).

Table 2 Guideline recommendations for BP lowering treatment in patients with acute ischaemic stroke who are not candidates for rtPA

	Start medication	Target
American Heart Association	BP >220 / 120 mmHg	Lower BP by 15 to 20%
National Stroke Foundation (Australia)	BP ≥220 / 120 mmHg	Up to 20% reduction

Table 3 Guideline recommendations for BP lowering treatment in patients with acute ischaemic stroke prior and after treatment with rtPA

	Start medication	Target
American Heart Association	BP >185 / 110 mmHg	BP <180 / 105 mm Hg
National Stroke Foundation (Australia)	BP >185 / 110 mmHg	

The most important neurological complications are swelling of the ischemic tissue causing mass effect; haemorrhagic transformation of the infarction with or without mass effect; and, less commonly, seizures.

Patients with major infarctions affecting the cerebral hemisphere or cerebellum are at high risk for complicating brain oedema and increased intracranial pressure. Measures to lessen the risk of oedema and close monitoring of the patient for signs of neurological worsening during the first days after stroke are recommended. Patients with acute hydrocephalus secondary to an ischaemic stroke most commonly affecting the cerebellum can be treated with placement of a ventricular drain. Decompressive surgical evacuation of a space occupying cerebellar infarction is a potentially lifesaving measure, and clinical recovery may be very good. Decompressive hemicraniectomy surgery for malignant oedema of the cerebral hemisphere may be life-saving, but the impact on morbidity is unknown.

ICH should be suspected in any patient who develops sudden neurologic deterioration, a decline in level of consciousness, new headache, nausea and vomiting, or a sudden rise in BP after thrombolytic therapy is administered, especially within the first 24 hours of treatment. In patients with suspected ICH, the rtPA infusion should be discontinued and an urgent non-contrast head CT or MRI scan should be arranged. Blood should be drawn for typing and cross matching, and measurement of prothrombin time, activated partial thromboplastin time, platelet count, and fibrinogen. No reliable data are available to guide the clinician in the choice of effective measures to control ICH in this setting. Current recommended therapy includes the infusion of platelets (6 to 8 U) and cryoprecipitate that contains factor VIII to rapidly correct the systemic fibrinolytic state created by tPA. The guidelines for the surgical treatment of ICH after fibrinolysis for AIS are the same as those followed for ICH in general, but should be initiated only after a sufficient infusion of platelets and cryoprecipitate has stabilized intracranial bleeding.

Recurrent seizures after stroke should be treated in a manner similar to other acute neurological conditions.

Despite the interventions that are described in this outline, the prognosis of such patients often is very poor. Many people would not want to survive if a devastating stroke would lead to a persistent vegetative state or other condition of devastating incapacity. An increasing number of patients have advanced directive statements that provide instructions about emergency treatment in a situation such as a massive stroke. Physicians should honour those directives.

In other circumstances, such directives may not be available, and the patient's neurological status usually precludes decision making. Occasionally, a guardian with medical power of attorney can make the decision. Otherwise, the physician should involve family members. The physician should provide clear information about the nature of the stroke, the prognosis, and the treatment options. The family should be given the opportunity to select or withhold medical interventions. In such situation, the medical care may emphasize measures to keep the patient comfortable and to support the family during the terminal aspects of the stroke.

4. RATIONALE FOR LOW –DOSE rtPA IN AIS

rtPA is the only approved treatment of AIS, licensed on the basis of the pivotal NINDS trial published in 1995,[4] where an i.v. dose of 0.9 mg/kg (10% bolus, 1 hour infusion, 90mg max. dose) within 3 hours of the onset of symptoms improved outcomes in carefully selected (and managed) patients. On the basis of a meta-analysis of this and several subsequent trials of rtPA,[6] the time criteria for rtPA has recently been extended to 4.5 hours. The totality of the evidence among ~4,000 patients randomised to different forms of thrombolysis is now strong for i.v. rtPA providing an overall net benefit despite having an increased risk of bleeding, most seriously of symptomatic intracerebral haemorrhage (sICH) (2-10%) but also of any ICH (20-30%),[7] arising either within the area of cerebral ischaemia/infarction (so-called 'haemorrhagic transformation') or elsewhere in the brain, manifest as anything from small petechial to overt lobar haemorrhage with mass effect. ICH, the most feared complication of rtPA, arises in part because rtPA has a prolonged action on thrombi in the body despite having only a short (mins) half-life in serum, and in part due to various alterations in blood flow and permeability within and around infarcted brain. Despite this risk, patients who receive rtPA early after the onset of AIS have an overall ≥30% relative increased chance of having little or no residual disability.[8] The treatment effect translates into 1 fewer patient dead or physically dependent for every 10 treated, 1 fewer dying per 100 treated, and 1 sICH per 14 treated.[8] Yet, as rtPA fails in up to 50% of patients due to there being a severe ischaemic deficit and/or slow and incomplete thrombolysis (i.e. re-canalisation), efforts continue to be made towards improving the efficiency of the treatment.[9] Clot-retrieval devices, used either alone or as an adjuvant to thrombolysis, have recently been shown to provide significant benefit to patients with AIS due to occlusion of large proximal cerebral vessels.[5] Conversely, there has not been any advance in finding a suitable alternative i.v. thrombolytic to rtPA, as older agents are not widely available (e.g. urokinase) or have uncertainty over dose and safety (e.g. streptokinase), and new agents have not established efficacy (e.g. desmoteplase).[56] *Thus, further trials of rtPA (e.g. IST-3,[1] results in 2012) with brain imaging, such as ENCHANTED, are still required to strengthen the evidence in important subgroups of patients (e.g. age >80 years, diabetes, and various brain scan parameters) to allow treatment to be tailored to individuals and increasingly more complex patients with acute stroke.*

Standard-dose rtPA was chosen on the basis of pilot dose-escalation studies. The first used doses of 0.35 (n=6), 0.60 (n=12), 0.85 (n=30), 0.95 (n=25) and 1.08 (n=1) mg/kg tested within 90 minutes of ischaemic stroke,[10] and showed that the proportion of patients with major neurological improvement at 24 hours was higher in the 0.85 mg/kg tier (55%) compared to the 0.6mg/kg tier (33%), and there were no sICH in doses <0.95 mg/kg. The second study used 0.6 (n=8), 0.85 (n=6) and 0.95 (n=6) mg/kg in patients 90-180 minutes after stroke, with 1 sICH occurring in each of 2 highest tiers.[11] A small placebo-controlled trial of 0.85 mg/kg had no sICHs in the treated group (n=14).[12] However, as emphasised by the investigators of these studies, the numbers of patients included were too small to reach any firm conclusion regarding the optimum dose of rtPA, and as outlined in a letter to *Stroke*,[13] a proposed trial to compare 0.6 to 0.9 mg/kg of rtPA was not approved for funding by the NINDS in the mid-1990s. Instead, the subsequent main NINDS[4] and ECASSII[14] trials (note: the first ECASS[15] showed that 1.1 mg/kg of rtPA was no more effective than placebo on neurological outcomes at 3 months due to higher rates of death and sICH in the rtPA group) went on to show that the 0.9 mg/kg dose provided benefits with an acceptable risk of sICH, so it become the standard approved dose of rtPA. However, subsequent studies have shown that thrombolysis is possible with a lower dose of rtPA, for example: (a) patients treated with combined i.v. and intra-arterial (i.a) rtPA and/or clot retrieval devices (e.g. the Interventional Management of Stroke [IMS] study[16]) do not always receive the full 0.9 mg/kg dose of rtPA, commenced as part of 'bridging therapy', because their subsequent cerebral angiogram fails to demonstrate a clot treatable by either thrombolysis or device, and; (b) *real-time transcranial ultrasound used during rtPA[9] shows early re-canalisation (median onset 17 minutes) often occurs prior to completion of the full 1 hour infusion of standard-dose rtPA.*

Low-dose (0.6 mg/kg) of rtPA was first evaluated in 3 small double-blind randomised controlled trials of duteplase (similar to rtPA) within 6 hours of acute ischemic stroke in Japan 20 years ago:[17-18] 20 mega-international units (MIU) of duteplase was superior to placebo; 20 MIU (equal to 0.33 MIU/kg or 0.6 mg/kg of rtPA) was comparable to 30 MIU on both angiographic re-canalisation and clinical improvement; and massive ICH was more frequent in patients who received 30 MIU. Low-dose rtPA has been used in Japan because of concerns that the standard dose has a higher haemorrhage risk in this population. Studies show racial differences in coagulation-fibrinolysis factors,[19] such as higher plasma concentrations of fibrinogen and plasminogen activator inhibitor among Caucasians than the Japanese,[19-20] and racial differences in genetic polymorphisms of coagulation factors.[21] Despite use of a lower dose of rtPA for acute myocardial infarction in Japan (0.5-0.75 vs 1-1.25 mg/kg), coronary artery patency rates appear comparable with other countries (60%-80%).[19] Thus, the Japan Alteplase Clinical Trial (J-ACT)[22] was undertaken with 0.6 mg/kg rtPA in an open non-randomised evaluation of patients within 3 hours of acute ischaemic stroke and showed equivalent clinical outcomes but a reduced risk of sICH compared to expected rates from the standard 0.9 mg/kg dose.[22] J-ACT and comparable data from subsequent registry studies in Japan[23-24] (and Taiwan[25]), led to approval of the 0.6 mg/kg dose as the standard treatment for patients with acute ischaemic stroke in Japan. However, this policy has caused considerable confusion in other parts of Asia, where there is continued uncertainty as to the balance of benefits and risks of low- versus standard-dose rtPA. This has led to the 0.9 mg/kg remaining the gold standard dose of rtPA but the 0.6 mg/kg dose (which may be require use of a single 50mg vial of Actylise ®Boehringer Ingelheim) becoming an attractive 'low-cost' 'cheaper' 'softer' option for patients who cannot afford the full dose (i.e. 2 vials). *The high cost of rtPA (~US$2,000 per 2x50mg vials for 0.9 mg/kg dose)[26] is a major out-of-pocket expense for many people in fee-for-service health care systems of low-middle income countries.[27]*

Low-dose rtPA appeared safe and effective but there was no reliable randomised evidence to support a widespread policy for its use in Asia or elsewhere in the world. Low-dose rtPA may be safer in Asians due to racial differences in coagulation factors, but any potential pharmaco-therapeutic differences among races in the response to rtPA may not be specific to the Japanese. For example, enhanced sensitivity to rtPA manifest by increased thrombolytic efficacy, systemic fibrinogen breakdown and need for transfusion has been noted among Black-American patients with acute myocardial infarction.[28] The effects of low-dose rtPA in Asians could simply be explained on the basis of a lower total dose comparable with a smaller body weight/mass, or that Asians have a lower 'clot volume' due to the greater proportion of small vessel occlusive or 'lacunar' forms of ischaemic stroke compared to more large vessel and cardio-embolic strokes (i.e. high clot volume) in non-Asians. Thus, standard-dose rtPA may be better in situations of older, harder, larger, fibrin-poor clot/thrombi arising from proximal extra-cranial atheroma or cardiac sources, whilst low-dose rtPA may be better and safer (i.e. lower risk of sICH[29]) for acute platelet-rich or low volume thrombi in more distal or smaller perforating cerebral vessels producing lacunar strokes. Of course, i.v. rtPA may not be effective at all in older, harder, larger, fibrin-poor clot/thrombi arising from proximal intra- or extra-cranial atheroma, or cardiac sources. Careful in vitro studies indicate no further increase in the degree of clot lysis above doses of rtPA equivalent to 0.6 mg/kg,[30] while non-randomised comparative clinical studies in Singapore suggest poorer outcomes from low- compared to standard-dose rtPA in patients with AIS, raising the issue of inferior re-canalisation with the lower dose.[31-32] As emphasised in the Cochrane review of thrombolysis in AIS, despite no clear differences being evident in indirect comparisons of different dose (or forms) of thrombolytic agents,[7] in the absence of head-to-head direct comparative studies, there was uncertainty over the relative benefits and risks of low- versus standard-dose rtPA. Thus, the current variable (ad-hoc) use of low-dose rtPA outside of Japan may be denying benefits (or exposure to unnecessary hazard) for many thousands of patients, so that if it could be *proven to be safe and effective, it could provide evidence to substantiate use of a low cost treatment for stroke in many parts of the world.*

5. SUMMMARY OF RATIONALE FOR LOW – DOSE rtPA IN AIS

rtPA is the only approved treatment of AIS despite increased risk of sICH. Recent studies suggest that low-dose of rtPA is an effective treatment and may have a reduced risk of sICH but there is lack of reliable randomised evidence to support a widespread policy for its use in Asia or elsewhere in the world. ENCHANTED was designed as a large-scale study to determine the overall balance of risks and benefits associated with the use of low-dose rtPA in patients with AIS. The main results of this arm of the study were published in the New England Journal of Medicine in 2016. [34]

6. EVIDENCE FOR EARLY INTENSIVE BP LOWERING AFTER rtPA IN AIS

The optimal management of BP in AIS remains controversial. Elevated BP or 'hypertension' (i.e. systolic >140 mmHg) is very common (>60%) early after the onset of AIS,[34-5] with the degree of increase in BP being greater in patients with pre-existing hypertension and larger strokes,[36,37] and levels tending to decline over the subsequent week. While generally positive associations between BP levels and poor outcomes are evident, very low (systolic <130 mmHg) BP levels and large reductions in BP are also related to poor outcomes in AIS.[5-36] Various explanations for elevated BP include acute physiological stress, pain, unstable pre-existing hypertension, or increased intracranial pressure, occurring in the context of a critical set of mechanisms operating in relation to the evolving cerebral ischaemia/infarction to produce varying degrees of cerebral oedema and haemorrhagic transformation from re-perfusion and collateral flow into the injured region of the brain. However, the observed U- or J-shaped relationship of BP and outcome[35-36] may not be causally related; rather patients with more severe strokes (and who naturally have worse outcomes) may have a more prominent autonomic response resulting in higher BP at presentation, and the same type of patients may also develop lower BP levels as their condition worsens, sometimes as a pre-terminal event. To complicate matters further, hypertensive patients appear to have their cerebral autoregulation shifted to a higher level, whereas in all patients the critically vulnerable penumbral rim of the infarct core of AIS, cerebral autoregulation is likely to be disrupted so that cerebral perfusion pressure is directly related to systemic BP.[37] Even so, experimental models of focal cerebral ischemia and reperfusion indicate that BP reduction reduces the size of cerebral ischaemia and improves reperfusion.[38] In the first IST study, the higher rate of death or dependency in patients (n=17,398) with initially high or low systolic BP within 48 hours of ischaemic stroke appears to have been mediated in part by increased rates of early recurrence and death from presumed cerebral oedema in patients with high BP and increased coronary artery events in those with low BP.[39] Finally, recent data indicate that wide fluctuations in BP early after AIS is associated with an increased risk of death, possibly due to altered perfusion pressure in the ischaemic penumbra exacerbating cerebral oedema or haemorrhagic transformation. *Any potential benefits of rapid BP lowering in AIS must be balanced against potential risks of worsening ischaemia from altered autoregulation and/or perfusion in the ischaemic penumbra. However, any risks of BP lowering appear to only at very low systolic BP levels (ie <130 mmHg)[40] which is beyond those outlined in the ENCHANTED protocol.*

More intensive BP lowering may reduce the risk of sICH after rtPA. Guidelines for BP control in AIS are consistent in contraindicating use of rtPA in patients with 'uncontrolled' BP according to the definitions used in the NINDS rtPA stroke study, that is with systolic BP >185 mmHg and diastolic BP >110 mmHg.[41] However, recent data have emerged to suggest that lower and more stable BP levels may improve outcomes, particularly in patients who receive rtPA. [40, 42] In the original NINDS study,[4] use of antihypertensive therapy was common in both the placebo and active groups, so although this treatment did not appear to influence outcomes, the small sample size (n=624) and lack of randomised variation precluded firm conclusions to be drawn on the role of BP control on the outcomes.[40] Subsequent non-randomised studies indicate that 'inadequate control' of BP (or pre-treatment BP rtPA protocol violations) prior to, and after, the use of rtPA is associated with a higher likelihood of sICH.[43-44] The most compelling data are from the large-scale prospective registry studies: the Safe Implementation of Thrombolysis in Stroke-Monitoring STudy (SITS-MOST)[45] of 6483 patients from 285 mainly European centres between 2002 and 2006; and the Safe Implementation of Thrombolysis in Stroke–International Stroke Thrombolysis Register (SITS-ISTR)[44] with expanded measures including serial BP (baseline, 2 and 24 hours), treatment and outcome data in 11,080 patients registered between 2002 and 2006. In SITS-MOST, elevated baseline systolic BP (odds ratio [OR] 1.3, 95% confidence interval [CI] 1.1-1.7 per 20 mmHg standard deviation) was associated with sICH, which occurred in 8.5% (95%CI 8-9%) according to the use of a strict definition. In SITS-ISTR, multivariable analyses showed that: elevated systolic BP levels (i) as a continuous variable was associated with a worse outcome (P<0.001) and (ii) as a categorical variable had a linear association with sICH and a U-shaped association for death and dependency such that the best outcome occurred in the nadir 141-150 mmHg; and sICH was 4 times higher in patients with a post-rtPA systolic BP >170 mmHg compared with those with levels of 141-150 mmHg. Moreover, withholding antihypertensive therapy for several days in patients with prior hypertension was associated with worse outcomes, whereas initiation of antihypertensive therapy in newly recognised cases of moderate hypertension was associated with a favourable outcome. *These data indicate that a ≥15 mmHg difference in systolic BP levels equates to ≥15% reduction in a poor outcome after rtPA.*

Completed and ongoing trials of early BP lowering in acute stroke Current guidelines for BP management in AIS highlight the need for a definitive study since their expert-derived recommendations provide only an indication of perceived harm from high BP, with arbitrary levels of <185 mmHg systolic BP before rtPA and <180mmHg after rtPA chosen to be achieved.[41] As emphasized by multiple editorials and reviews,[34,46-47] the management of elevated BP in AIS is a major research question that needs to be resolved. None of the major trials in this area (e.g. the Scandinavian Candesartan Acute Stroke Trial [SCAST][48]) and Efficacy of Nitric Oxide in Stroke (ENOS)[36-39] in the area have been specifically designed to address the role of very early (i.e. within a few hours), rapid and intensive (i.e. i.v. agents) BP lowering, and most importantly, as to whether such treatment improves outcomes and reduces the risk of ICH after rtPA. *The INTERACT2 study[49-50] showed that rapid BP lowering (140 mmHg systolic target) was feasible, safe and potentially efficacious improving outcome after ICH, provides a strong rationale and an appropriate time to test the effectiveness of the treatment protocol with rtPA in AIS.*

7. CHOICE OF BP PRESSURE LOWERING AGENT

There are a number of different drug classes that may be used to lower BP in acute stroke, and each has potential advantages and disadvantages. It is uncertain which class of BP lowering agent is most desirable in the acute phase of stroke and there are different routes of administration. Effective oral treatment cannot be guaranteed during the acute phase of stroke because of the frequent occurrence of dysphagia and/or reduced levels of consciousness, which is seen in up to 50% of patients. In addition, the early insertion of a naso-gastric tube may not be possible, and it is often pulled out by confused patients. Whilst transdermal administration might be useful, the onset of a BP lowering effect is slow and produces only a modest effect, which is less desirable in patients with severe hypertension. Intravenous treatment is the optimal route of administration during the acute phase of acute ischaemic stroke as it allows rapid BP reduction and in a titratable manner. However, intravenous treatment requires close monitoring of BP levels in patients to avoid hypotension, but this is readily accomplished within acute stroke units, high dependency units, or intensive care unit. **Table 4** lists various intravenous medications for BP lowering, their profile of action and potential adverse effects.

Table 4 Possible intravenous medications for BP lowering

Drug	Onset	Duration	Potential adverse effects
Esmolol	5-10 min	10-30 min	Hypotension, nausea, asthma, first-degree heart block, heart failure
Labetalol	5-10 min	3-6 h	Vomiting, scalp tingling, bronchoconstriction, dizziness, nausea, heart attack, orthostatic hypotension
Urapidil	5-10 min	3-4 h	Dizziness, nausea, palpitations, orthostatic hypotension
Phentolamine	1-2 min	10-30 min	Tachycardia, flushing, headache
Clonidine	10-20 min	3-6 h	Sedation and other central nervous system effects, dry mouth, discontinuation syndrome
Nicardipine	5-10 min	15-30 min	Hypotension, tachycardia, headache, flushing, local phlebitis
Hydralazine	10-20 min	1-4 h	Hypotension, tachycardia, flushing, headache, vomiting, aggravation of angina
Nitroglycerin	2-5 min	5-10 min	Headache, vomiting, methaemoglobinaemia, tolerance with prolonged use
Enalaprilat	15-30 min	6-12 h	Precipitous fall in pressure in high-renin status
Nitroprusside	Immediate	1-2 min	Hypotension, nausea, vomiting, muscle twitching, sweating, thiocynate and cyanide intoxication
Clevidipine	2-10 min	10 min	Hypotension, tachycardia, lipid overload

Amongst these agents, sodium nitroprusside is arguably the least desirable for routine use outside of an intensive care unit because of its potent anti-platelet effects, ability to increase intracranial pressure, and profound BP lowering effects.

Guidelines only recommend use of sodium nitroprusside in patients with extremely high BP levels. Intravenous infusions of the other short acting agents are more desirable for close control of BP. Labetalol is recommended in the AHA Guidelines and is widely available in most countries throughout the world, a notable exception being Australia. The alpha adrenergic antagonists urapidil hydrochloride, frusemide and phentolamine are popular in China. These drugs can both be used initially as bolus injections, followed by infusions.

8. SUMMARY OF RATIONALE FOR A TRIAL OF BP LOWERING IN AIS

Current guidelines for BP management in AIS highlight the need for a definitive study since their expert-derived recommendations provide only an indication of perceived harm from high BP. The management of elevated BP in AIS is a major research question that needs to be resolved. None of the recently completed and ongoing trials in the area have been specifically designed to address the role of rapid intensive BP lowering within the first few hours of onset, and in particular, as to whether such treatment improves outcomes after rtPA.

AIMS AND OBJECTIVES

In patients with AIS eligible for thrombolysis using rtPA according to local guidelines and otherwise able to receive best usual medical care.

1. PRIMARY AIMS

[A] Compared with standard dose i.v. rtPA, low-dose rtPA is at least as effective ('not inferior') on the major clinical outcome of death or disability at 3 months (i.e. corresponding null hypothesis is that low-dose is inferior to standard dose rtPA) (Results published in May 2016);

[B] Compared with standard guideline-based BP management, early intensive BP lowering is *superior* in improving functional recovery according to a comparison of ordinal scores on the mRS at 3 months (i.e. corresponding null hypothesis is that there is no difference in treatments on this outcome).[49]

2. KEY SECONDARY AIMS

[C] Compared with standard dose i.v. rtPA, low-dose rtPA reduces the risk of sICH (Results published)

[D] Compared with standard guideline-based BP management, early intensive BP lowering after thrombolysis with rtPA reduces the risk of any ICH (i.e. corresponding null hypothesis is that there is no difference in the rate of any ICH between groups of differing intensities of BP lowering).

3. OTHER SECONDARY AIMS

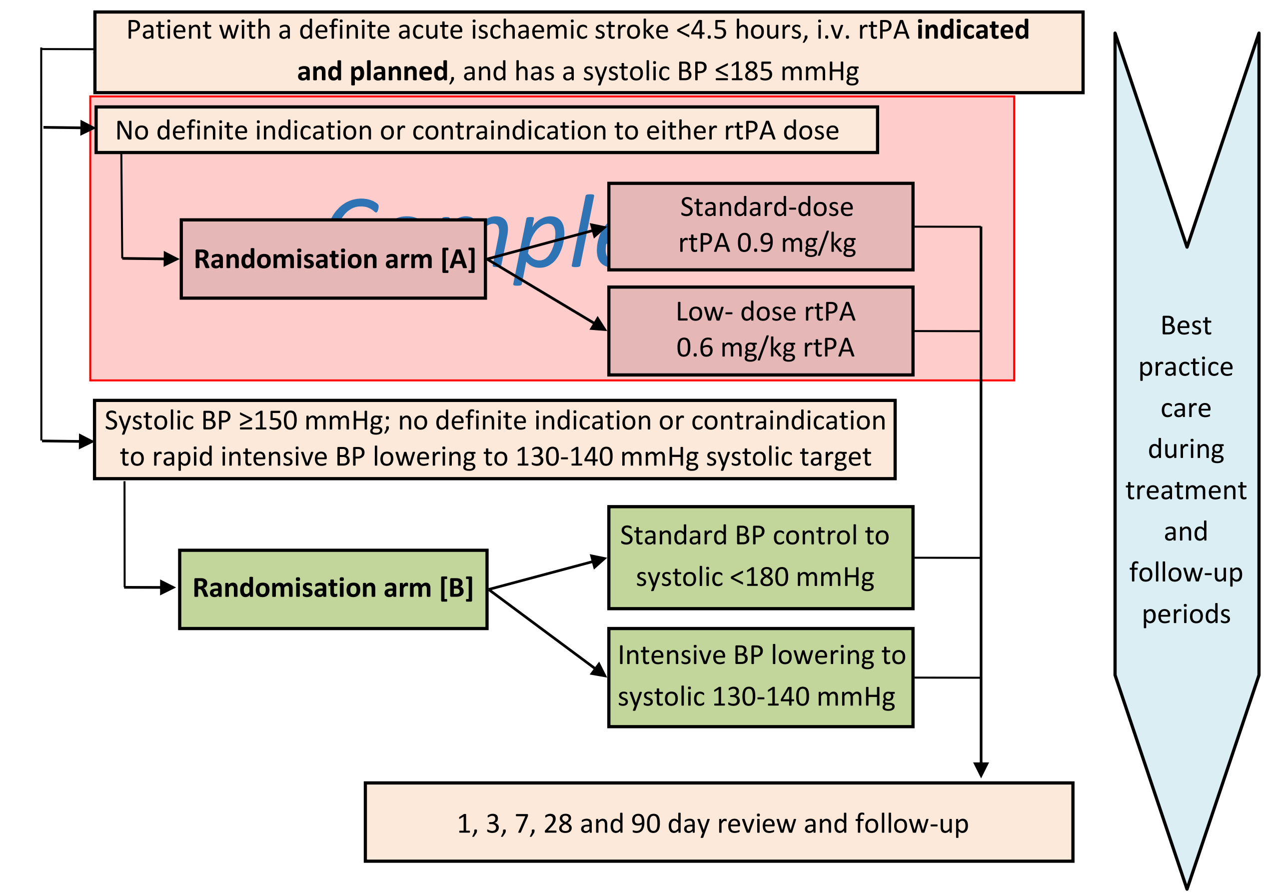
To define effects on a shift ('improvement') in measures of disability according to the grading system on the modified Rankin Scale (mRS) in arm [A];[51] sICH; good recovery (mRS 0-1); death or major disability (mRS 3-6); separately on death and disability (mRS 3-5); early neurological deterioration; HRQoL; length of hospital stay; need for permanent residential care; and health care costs.

METHODS

1. OVERALL DESIGN

This study is an international, multicentre, prospective, fixed-time point (optional) randomisation for two arms (**[A]** **'**dose of rtPA' and **[B]** 'level of BP control'), open, blinded endpoint (PROBE), controlled trial that will involve 4500 patients (3300 for arm **[A]** and 2100 for arm **[B]** with overlap of 939 patients) with AIS recruited from over 100+ Clinical Centres from Australia, Asia, Europe and South America. The study design is summarised in the following schema.

Study schema



2. STUDY POPULATION

All patients presenting to participating centres with suspected AIS arriving <4.5 hours of symptoms onset will be considered for this trial. Primary responsibility for recruitment of patients will lie with the Principal Investigator (PI) at each centre. It is anticipated that successful recruitment will require the active involvement of Emergency Department staff at each centre, since rapid referral of patients early after stroke onset is required. Rate limiting steps after presentation are anticipated to include the time taken for:

(1) completion of brain imaging (CT brain or MRI);
(2) receipt of informed consent and baseline assessment; and
(3) administration of randomised treatment.

In order to facilitate recruitment, study centres should aim for a ‘door-to-needle’ time of 60 minutes, which is in line with current guidelines for effective use of rtPA, and a randomisation-to-treatment time of 15 minutes.

3. INCLUSION AND EXCLUSION CRITERIA

To be eligible for inclusion in this study, patients must fulfil local criteria for the routine use of i.v. rtPA, and the attending clinician is required to consider their level of clinical uncertainty over the balance of potential benefits and risks pertaining to the level of BP control in each particular patient, as outlined below.

1. *General criteria for use of thrombolytic treatment with rtPA.*
   (a) Adult (age ≥18 years)
   (b) A clinical diagnosis of acute ischaemic stroke confirmed by brain imaging
   (c) Able to receive rtPA treatment within 4.5 hours after the definite time of onset of symptoms
   (d) Have a systolic BP ≤185 mmHg within 6 hours of symptom onset (i.e. the guideline recommended level of eligibility for rtPA; patients with higher BP levels at presentation can still be included provided the BP is reduced to the entry level prior to commencement of the treatment)
   (e) Provide informed consent (or via an appropriate proxy, according to local requirements)
2. *Specific criteria for intensive BP lowering vs guideline recommended BP control.*
   (a) Patient will or has received routine thrombolysis treatment with rtPA, according to physician-decided dose rtPA
   (b) Sustained elevated systolic BP level, defined as 2 readings ≥150 mmHg
   (c) Able to commence intensive BP lowering treatment within 6 hours of stroke onset.
   (d) No definite indication or contraindication to either immediate 'intensive' BP lowering (to a target of 130-140 mmHg systolic) versus guideline-based BP control (e.g. intensive BP lowering is feasible and does not appear to pose excessive hazard to the patient).

Patients will **NOT** be eligible if there is one or more of the following:
   (a) Unlikely to potentially benefit from the therapy (e.g. advanced dementia), or a very high likelihood of death within 24 hours of stroke onset.
   (b) Other medical illness that interferes with outcome assessments and follow-up [known significant pre-stroke disability (mRS scores 2-5)].
   (c) Specific contraindications to rtPA (Actilyse) or any of the blood pressure agents to be used.
   (d) Participation in another clinical trial involving evaluation of pharmacological agents
   (e) Need for following concomitant medication, including phosphodiesterase inhibitors and monoamine oxidase inhibitors.

4. ETHICAL ISSUES

This study will be conducted in compliance with the principles outlined in the World Medical Association's Declaration of Helsinki **(see Appendix 5)**.

4.1 Institutional Ethics Committee Approval

Each participating centre must obtain written approval(s) from their Hospital Research Ethics Committee (e.g. Institutional Review Board [IRB]), and other regional or national regulatory bodies before patient recruitment can commence. Any protocol amendments, serious adverse event (SAE) reports and routine reporting to the IRB will be the responsibility of the Principal Investigator (PI) at each participating centre.

4.2 Consent

The majority of patients admitted with AIS require emergency care. Some aspects of this care are thrombolytic treatment with rtPA and management of hypertension which needs to be treated urgently. However, the nature of this acute condition means that the patient may be too unwell to comprehend the information that must be given in the consent process and this consent needs to be obtained swiftly to avoid delays in urgent treatment. The optional consent procedures for this study are detailed below and should be followed according to local IRB guidelines.

Patient Consent

Wherever possible, the patient will be approached to directly give written informed consent. An information statement will be given to the patient and the implications for consenting to the study will be explained by a clinician familiar with the study protocol.

Person Responsible Consent

If the patient is not fully competent to give informed consent, for example because of a reduced level of consciousness or confusion, the patient's 'person responsible' will be approached to provide informed consent on his or her behalf.

Under the Guardianship Act of 1987 in New South Wales, Australia, a 'person responsible' are the legally appointed guardian, their spouse or de-facto spouse or same sex partner, or if there is none, their unpaid carer, or if there is none, their relative or friend who has a close relationship with the person.

The patient will be made aware of this process as soon as they are well enough and have an opportunity to withdraw the consent. If willing to continue participation in the study, the patient will be asked to sign their own consent form.

If the patient is dying or is still unable to record their personal consent by the time of completed follow up on the study, the consent given by their person responsible will stand and trial data will be retained. The reason for not obtaining the patient's consent will be documented, dated and signed in the patient's file.

If a patient is discharged from hospital before it has been possible to gain personal consent, the PI will make attempts to inform the patient of the study and gain written consent. If this has been unsuccessful after a minimum of 3 documented occasions, the consent given by their person responsible will stand and the trial data will be retained. The reason for not obtaining the patient's consent will be documented, dated and signed in the patient's file.

Guardianship tribunal consent

In the situation where a patient is unable to give consent and a 'person responsible' is not available or cannot be contacted, clinicians should seek guardianship tribunal approval before enrolling eligible patients in the study. The patient will be made aware of this process as soon as they are well enough and have an opportunity to withdraw the consent. If willing to continue participation in the study, the patient will be asked to sign their own consent form. If the patient is not fully competent to give informed consent, for example because of a reduced level of consciousness or confusion, the patient's 'person responsible' will be approached as soon as possible to provide informed consent on his or her behalf.

In the case of a patient's death, the PI should use discretion on a case by case basis before contacting the 'person responsible' in recognition of the potential distress that may exist as the result of a death. In either case, an explanation of the lack of patient or surrogate consent will be document in the patient's file.

Delayed consent

The circumstances surrounding emergency care research are such that it may not always be possible to obtain consent from either the patient or next of kin without delaying the initiation of treatment, and therefore risk reducing any potential benefits to the patient. In the situation where a patient is unable to give consent and a next of kin or other person responsible is not available or cannot be contacted, clinicians may enrol eligible patients and inform the patient or their person responsible for the patient as soon as possible so that delayed consent can be requested. The reasons for being unable to obtain prior consent will be documented, dated and signed in the patient's file.

If the patient should die or continue to be unable to give informed consent at the end of the trial follow up period, the next of kin or person responsible should be approached to obtain delayed written consent. In the case of a patient's death, the PI should use discretion on a case by case basis before contacting the next of kin or surrogate, in recognition of the potential distress that may exist as the result of a death. In either case, an explanation of the lack of patient or person responsible consent will be document in the patient's file.

Delayed consent in a clinical trial of emergency care is considered by the World Medical Association in the Declaration of Helsinki. This document states:

> "*Research on individuals from whom it is not possible to obtain consent, including proxy or advance consent, should be done only if the physical/mental condition that prevents obtaining informed consent is a necessary characteristic of the research population*."

This study includes such potentially eligible patients.

The Australian NHMRC also gives guidance to human research ethics committees on this issue:

> "*When the nature of the research procedure is such that conformity to the principle of consent is not feasible, and neither the individual nor the individual's representative can consider the proposal and give consent in advance, a Human Research Ethics Committee (HREC) may approve a research project without prior consent provided it is satisfied that:*
>
> *(a) inclusion in the research project is not contrary to the interests of the patient; and*
>
> *(b) the research is intended to be therapeutic and the research intervention poses no more of a risk than that which is inherent in the patient's condition and alternative methods of treatment; and*
>
> *(c) the research is based on valid scientific hypotheses which support a reasonable possibility of benefit over standard care; and*
>
> *(d) as soon as reasonably possible, the patient and/or the patient's relatives or legal representatives will be informed of the patient's inclusion in the research and of the option to withdraw from the research without any reduction in quality of care".*

All four criteria apply to this study protocol including the uncertainty about the optimal rtPA dose and BP management in the medical profession and the current guidelines.

Withdrawal of Consent
The information statement provided to the patient and/or the next of kin or surrogate will clearly state that the patient can be withdrawn from the study at any time without prejudice and explanation. Such withdrawal should be documented in the patient's file. If withdrawal of consent relates to the BP management alone, data collection can continue on documentation of this fact in the patient's files.

4.3 Confidentiality and privacy

Every precaution should be taken to respect the privacy of patients in the conduct of the study. Only de-identified data will be submitted to the ICC at The George Institute for Global Health to maintain patient confidentiality. However, in the course of monitoring data quality and adherence to the study protocol the study monitor will refer to medical records at the participating hospital.

5. RANDOMISATION

After confirmation of eligibility, patients are randomised via a central internet-based system at The George Institute, Sydney, Australia, either direct or via a specially developed Interactive Voice Randomisation System (in China). This will be done by connecting the study centre (e.g. emergency department or stroke unit) to the server at the ICC where the patient will be registered and the randomised treatments will be assigned for that particular patient.

The randomisation sequence will use a minimisation algorithm to ensure balance in key prognostic factors. Patients will be stratified according to:

1. site of recruitment
2. time from onset <3 hours versus ≥3 hours;
3. NIHSS score <10 versus ≥10;

From August 2015, the study allows patients only to be allocated to arm **[B]** 'level of BP control' only:

- intensive BP lowering to a target systolic BP range 130-140 mmHg within 60 minutes of Randomisation into the BP arm and to maintain this level for at least 72 hours (or until hospital discharge or death if this should occur earlier) or guideline-based BP lowering to a target systolic BP of <180 mmHg post-rtPA.

6. ALLOCATED STUDY TREATMENTS

From August 2015, the attending clinician is required to consider their level of clinical uncertainty over the balance of potential benefits and risks pertaining to the level of BP control in each particular patient. Investigators are encouraged to adhere to study protocols, provide active care, but are free to modify a patient's treatment as required according to clinical judgment.

6.1 BP control arm

6.1.1 Early Intensive BP Lowering Group
The aim is to achieve a systolic BP level 130-140 mmHg **within 60 minutes** of Randomisation into the BP arm *and* to maintain this BP level for the next 72 hours (or until hospital discharge or death if this should occur earlier). A standardised i.v. BP lowering regimen using locally available and approved i.v. BP lowering agents will be used, commenced in the emergency department and later in a high dependency area (e.g. acute stroke or neurointensive care unit) as is usual for patients receiving rtPA.

BP lowering will be titrated by repeat i.v. bolus or infusion, with a systolic BP of <130 mmHg being the safety threshold for cessation of therapy. It is anticipated that i.v. agents will be required for at least the first several hours in most cases but the timing of switch to oral BP lowering agents will be at the discretion of the responsible clinician according to BP control and patient status. It is also expected that i.v. therapy will continue to be required during the initiation of oral anti-hypertensive therapy, to maintain the systolic BP levels 130-140 mmHg.

When administering BP lowering treatment, care is required to ensure that severe hypotension is avoided in patients by checking first for potential dehydration and providing intravenous fluids.

Since the study 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, some flexibility is allowed in the use of locally available i.v. agents (e.g. urapidil, labetolol, hydralazine, metoprolol, clevidipine), but all other aspects treatment are standardised across sites. Patients on prior oral BP lowering agents should have this continued if possible and antihypertensive therapy prescribed when patients are clinically stable as per guidelines for secondary stroke prevention. Investigators are encouraged to adhere to study protocols, provide active care, but are free to modify a patient's treatment as required according to clinical judgment.

<u>Intravenous treatment protocol</u>
Intravenous treatment protocols, based on available medications, are provided in **Appendices 1A to 1H**. The intravenous treatment will be titrated against regular BP monitoring to achieve a target systolic BP range (130-140 mmHg) within 60 minutes. It is anticipated that intravenous control of systolic BP will be required for at least the first several hours.

<u>Oral treatment protocol</u>
The switch from intravenous to oral BP lowering treatment will be made at the discretion of the responsible physician, depending upon the control and stability of the BP and the clinical status of the patient. It is anticipated that oral treatment will be started by 24 hours. An oral treatment protocol is provided in **Appendices 1A to 1H.** Combination treatment with an ACE inhibitor and diuretic will be recommended on top of other therapy as the first line oral treatment on the basis of the results of the PROGRESS trial and established best practice for the long-term prevention of BP-related events in patients with cerebrovascular disease.

The oral treatment protocol will also include a defined strategy for titration of treatment to achieve effective early systolic BP control once oral treatment is commenced. If the patient is unable to swallow, treatment should be administered via nasogastric tube.

For the intervention group, the goal is to maintain systolic BP levels within (130-140 mmHg) for 72 hours of hospital stay. If the patient is transferred to another hospital facility within 72 hours, then attempts should be made to continue therapy to achieve the systolic BP target of (130-140mmHg). The target systolic BP after hospital discharge remains <140 mmHg, as per guideline-based recommendations for high risk vascular disease patients. BP levels will be reviewed at 28 days follow-up and medication adjusted as necessary to maintain systolic BP <140 mmHg.

6.1.2 Control / Conservative BP Management Group
Patients allocated to the control group will receive management of BP that is based on a standard guideline, as published by the AHA (refer to **table 3** in Background section). **Appendix 1I** outlines the protocol for Control patients. For this group, the attending clinician may consider commencing BP treatment if the systolic level is greater than **180 mmHg**, however and the first line treatment will be oral (including nasogastric if required) and/or transdermal routes or according to local regulatory approval if applicable. Should control of systolic BP not be achieved via these routes, i.v. treatment may be started until the target

systolic BP of 180 mmHg is achieved. The oral and i.v. agents used will be the same as in the intensive BP lowering group as detailed in **Appendices 1A to 1H.** Oral anti-hypertensive therapy may be started at any time the treating physician feels the patient is stable. Oral therapy must be started by Day 7. The target systolic BP after hospital discharge is <140 mmHg, as per guideline-based recommendations for high risk vascular disease patients.

6.2 Previous Use of Antihypertensive Therapy in Both Groups

Patients who have been taking antihypertensive therapy prior to randomisation will have their usual medication continued when oral administration is possible, unless the agents are considered to be inappropriate by the responsible physician (e.g. poor compliance, intolerance, or adverse events). Otherwise, based on the results of the PROGRESS trial, a combination of an ACE inhibitor and diuretic should be added to any existing antihypertensive therapy when the patient is considered medically stable.

7. DISCONTINUATION OF ALLOCATED MANAGEMENT POLICY

The investigator must not deviate from the protocol except the patient/surrogate chooses to withdraw consent to participation in the study. However, allocated management in either group should be discontinued or modified if any of the following occur:

a. SAEs, which are in the opinion of the investigator, related to the trial protocol (refer to appropriate section for definitions).
b. The investigator feels it is in the subject's best interest.

Follow-up data will be collected for all treated subjects except those who specifically withdraw consent for release of such information.

8. BACKGROUND CARE

All patients will be managed in a facility with an adequate nurse/patient ratio and capacity for repeated neurological examination and non-invasive BP and heart rate monitoring (consistent recordings using automatic devices, every 15 minutes for 1 hour, then 6 hourly for 24 hours, then twice daily for 1 week). All BP measurements are from the non-paretic arm (or right arm in situations of coma or tetraparesis), with the patient resting supine for ≥3 minutes. All patients are to receive active care and best practice management according to guidelines, and neurointervention with intra-arterial thrombolysis and/or mechanical clot retrieval is still allowed according to local practice.

An acute stroke unit is defined as an area that:

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

During the study treatment and follow-up period, the usual management of acute stroke patients will be followed according to published guidelines **(see Appendix 4)** for the acute stroke care protocol. It is anticipated that background care may include significant use of treatments including drugs and endovascular intervention. Use of other therapies will be documented and compared between countries and should be balanced between randomised groups.

9. STUDY OUTCOMES

Primary outcome for arm [A] was the combined endpoint of death and disability as defined by the conventional dichotomised '0-1' versus '2-6' cut-point on the mRS[51] at 3 months. *Primary outcome for arm [B]* is a comparison of ordinal shift in scores on mRS at 3 months.[52,53] The mRS is a widely used instrument for grading the impact of stroke treatments,[48] with scaling of: 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.

Secondary outcomes are: (a) symptomatic ICH based on NINDS criteria of brain imaging (or necropsy) confirmed ICH with ≥1 points deterioration in NIHSS score or death within 36 hours from baseline; (b) symptomatic ICH, defined by SITS-MOST criteria,[45] as large ('type II') parenchymal ICH with ≥4 points decline in NIHSS score or death within 36 hours from baseline; and (c) ICH of any type in brain imaging ≤7 days of treatment; (d) good outcome, defined by scores 0-1 on the mRS (e) death or major disability, defined by scores 3-6 on the mRS, (e) death, (f) disability (mRS score 3-5), (g) neurological deterioration ≥4 points decline in NIHSS score over 72 hours, (h) HRQoL by the EuroQoL,[54] (i) admission to residential care, and (j) health service use for calculation of resources and costs.

RESULTS AND OUTCOME OF ARM [A]

In arm [A], the primary outcome occurred in 855 of 1607 participants (53.2%) in the low-dose group and in 817 of 1599 participants (51.1%) in the standard-dose group (OR 1.09; 95% CI 0.95 to 1.25; the upper boundary exceeded the noninferiority margin of 1.14; P = 0.51 for noninferiority). Low-dose rtPA was noninferior in the ordinal analysis of mRS scores (unadjusted common OR 1.00; 95% CI 0.89 to 1.13; P = 0.04 for noninferiority). Major sICH occurred in 1.0% of the participants in the low-dose group and in 2.1% of the participants in the standard-dose group (P = 0.01); fatal events occurred within 7 days in 0.5% and 1.5%, respectively (P = 0.01). Mortality at 90 days did not differ significantly between the two groups (8.5% and 10.3%, respectively; P = 0.07). Conclusion: In patients with AIS low dose rtPA was not shown to be noninferiority of standard-dose rtPA with respect to death and disability at 90 days. However, there were significantly fewer sICH and deaths with low-dose rtPA.

10. DATA COLLECTION AND FOLLOW-UP

Registration, baseline assessment, and randomisation should be achieved over 30 minutes. Doctor/nursing attendance with the randomised patient is likely to be required for 1-2 hours post-randomisation to ensure safe and effective thrombolysis, the titration of BP lowering in the active group, and consistent BP recordings. All patients are followed daily for 1 week and then at 28 and 90 days unless death occurs earlier. Investigators will be reimbursed for their time involved in data collection and for local expenses (e.g. printing, internet connection, purchase of medications, copying of brain imaging (CT scans and/or MRIs). Data collection will be kept to a minimum to ensure rapid enrolment and follow-up of patients within the context of routine clinical practice. Key demographic and clinical data will be collected at randomisation. Follow-up data will be collected on 5 occasions: 24 and 72 hours, and 7 (or hospital discharge if sooner), 28 and 90 days. The 28 and 90 day evaluations will be conducted in-person or by telephone, by a trained staff member at the local site who is blind to the treatment allocation. Original records entered directly into database, e.g. data entered directly into database from patient interview or assessment, are acceptable as source data. Brain imaging (CT scan and/or

MRI, with any associated diffusion/perfusion and angiogram images) will be conducted according to standardised techniques at baseline, within 24 hours (ie next day follow-up scan), and at a later stage in all surviving patients who may deteriorate or for other clinical reason during follow-up. Brain imaging (CT scan and/or MRI) must be uploaded to the ENCHANTED server, either directly from the hospital site (if they have suitable broadband internet) or via the RCC office, to be analysed centrally for measurement of any ICH or haemorrhagic complications of the ischaemic lesion, and for future measurement of areas of infarction, ischaemic, penumbra, sites of vessel occlusion. The LCC will keep a hard copy in an uncompressed DICOM format onto a CD-ROM for monitor site verification. Trial management is facilitated by an established internet-based system.

All randomised patients will be followed up to 90 days, or death if prior to 90 days. Patients who do not follow the protocol and/or discontinue allocated management should still be followed up to 90 days as their data will be analysed on the 'intention to treat' principle. **Table 5** illustrates the schedule and nature of the data collection required during the study period. The paper version of the case report forms (CRFs) will be supplied with the procedure manual, as a reference only, together with a guide to completion of each data element and a definition of terms.

All data entry will be completed on a password protected study website. This web-based data management system will allow for real time data query generation for values entered outside of pre-set valid ranges and consistency checking. This system will speed up data reporting and assist overall trial management for all participating centres. In addition to the web-based data entry, BP and drug usage will also be recorded on a paper CRF at the patient's bedside as part of the patient's usual medical record management.

10.1 Screening logs

Each LCC should keep log of all patients presenting to their institution with a diagnosis of acute ischaemic stroke and who were considered for the study but subsequently excluded. The screening log will record patients' initials and date of admission together with a brief description of the main reason as to why a patient was not randomised. The log will be used by the Research Coordinator, PI and the ICC to monitor recruitment and to identify specific barriers to randomisation of eligible patients. It is also a requirement for the reporting of results of clinical trials.

10.2 Patient Contact Details log

Each centre will keep a record of the contact details and information of next-of-kin for all randomised patients. This will be kept at the participating centre in a locked filing cabinet and in accordance with local policies on the custody of confidential clinical trial data. The Patient Contact Details Log will also be used to document any issues arising from the consent procedure, attempts at follow up and information on protocol violations. The Patient Contact Details Log will be used by the Research Coordinator and PI in managing the consent process, follow-up schedule, and in responding to queries from the ICC.

10.3 Randomisation assessment

All patients admitted with AIS will be assessed by the responsible physician for eligibility to the study using a checklist of the eligibility criteria described previously. This form will be kept at the participating site in a locked filling cabinet with the study patient's file.

10.4 Baseline Data

The following information is to be collected on admission:

- Medical history
- Medications at time of admission
- BP, Heart rate (HR), Body weight and scores on the GCS and NIHSS
- Brain imaging findings to confirm the diagnosis of AIS
- Management with neurointervention if performed
- Baseline blood tests
- rtPA details
- Pattern of neurological deficits

All baseline and follow-up brain imaging (CT scans and/or MRI) is to be copied in an uncompressed DICOM format onto a CD-ROM to be uploaded to the ENCHANTED server, either direct from the site or via the RCC. The CD-ROM copy must be kept in the site for monitoring visit **(see Appendix 2).**

10.5 Follow up Data

Day 1 (from randomisation)
The primary goal of assessments within the first 24 hours will be to ensure adherence to the allocated ‘rtPA dose’ and/or ‘BP management’ protocol. BP and administered medication will be recorded. BP will be recorded supine in the non-paretic arm from the automated, electronic device used at the Clinical Centre. After the commencement of rtPA, BP will be recorded every 15 minutes for the first hour, then hourly from 1 hour to 6 hours, and 6 hourly from 6 hours to 24 hours. After the commencement of BP lowering treatment, BP will be recorded every 15 minutes for the first hour. When intravenous boluses are given, HR and BP should be re-checked and recorded 5 and 15 minutes later. In addition, the number of systolic BP excursions <140 mmHg, and minimum and maximum systolic BP levels in the first 24 hours, will be recorded. The following information will be recorded.

- BP
- BP lowering medication
- GCS and NIHSS scores at 24 hours
- Follow up brain imaging (CT brain or MRI) should be undertaken within 24 hours after baseline brain imaging and results recorded
- If other imaging investigations are performed (i.e. transcranial doppler), these should be documented in the CRFs
- Follow up blood tests
- Standard stroke care assessment

Day 3
At day 3, the goal will continue to ensure adherence to the allocated BP management protocol. BP levels will be recorded twice a day after the first 24 hours. The following information will be recorded:

- BP
- GCS and NIHSS scores
- Standard stroke care assessment

Day 7
On day 7 or on the day of hospital discharge/transfer or death if prior to day 7, the contact details of the patient or caregiver should be confirmed to facilitate follow up assessments. The following information will be recorded:

- BP
- BP lowering medication (medications used during day 2 to day 7)
- Disability assessed with the mRS
- Standard stroke care assessment
- Date of discharge from hospital if this should have occurred at this time

Day 28 and Day 90

These assessments are to be undertaken by an investigator who was not involved in the clinical management of the patient, and blind to the randomised treatment allocation. On 28±3 days and 90±7 days, all surviving patients will be evaluated through a telephone interview or at a face-to-face consultation. Use of BP lowering agents will be recorded **(see Appendices 1A to 1C)**. In addition to the mRS, HRQoL (using the EQ 5D) will be assessed.

Death

Patients who have died prior to any of the above scheduled assessments, cause of death documentation will be collected with date and time of death. Copies of post-mortem reports, hospital record entry or death certificate, should be kept with the Patient Contact Details log to assist in trial monitoring by the ICC.

Withdrawal of allocated management and protocol violations

A form will be provided to record the date and circumstances surrounding any deviation from the protocol or missed assessments.

Consent

Consent will be documented in the patient's progress notes and CRF and the type(s) of consent obtained will also be recorded on the database.

Serious Adverse Events (SAEs)

All SAEs will be recorded on the SAE form, and completed on the electronic CRF or faxed/emailed from a printed form to the ICC within the prescribed time. Additional information may be requested to provide supplementary information on the event and outcome.

Table 5 Schedule of evaluations

Evaluation	Prior to Randomisation	Day				
		1/2	3[a]	7[a]	28[b]	90[b]
Eligibility	**X**					
Brain imaging (CT or MRI ± angiogram)	**X**	**X**				
BP	**X** BP x 2	**X** ** For time points see the footer	**X** 12 hourly	**X** 12 hourly		
Heart rate	**X**					
Consent (a)	**X**					

Evaluation	Prior to Randomisation	Day				
		1/2	3[a]	7[a]	28[b]	90[b]
Clinical history prior medications	X					
Body weight (kg)	X			X		
Physical exam GCS/NIHSS	X	X	X			
Functional assessment with mRS				X	X	X
HRQoL assessment with EQ 5D					X	X
Routine blood tests	X	X				
BP lowering treatment		X	X	X	X	X
Standard stroke care		X	X	X		
Hospitalised or not				X	X	X
Contact details for Follow-up		X		X		

**

Q 15 min for 1 hour after initiation of rtPA

Q 15 min for 1 hour after initiation of BP lowering

Hourly from 1 hour to 6 hour after initiation of rtPA

6 hourly from 6 hour to 24 hour after initiation of rtPA

At any point where intravenous bolus drugs are administered, BP and HR should be recorded 5 and 15 minutes later.

(a) Or the day of discharge if prior to day 7,

(b) Information collected at a face to face consultation or through a telephone interview

11. SERIOUS ADVERSE EVENTS (SAEs)

11.1 Definitions

The mechanisms for reporting and notifying SAE are based on the guidelines of the International Conference on Harmonisation Good Clinical Practice (ICH-GCP). As defined by the WHO International Drug Monitoring Centre (1994):

A SAE is any untoward medical occurrence that:

- results in death
- is life threatening in the opinion of the attending clinician (ie the patient was at risk of death at the time of the event; it does not refer to an event that might hypothetically have caused death had it been more severe)
- requires inpatient hospitalisation or prolongation of existing hospitalisation
- results in persistent or significant disability or incapacity

- results in congenital anomaly or birth defect (Note that the females in the study population are likely to be post-menopausal)
- is an important medical event in the opinion of the attending clinician that is not immediately life-threatening and does not result in death or hospitalisation but which may jeopardise the patient or may require intervention to prevent one of the other outcomes listed above

An **unexpected adverse reaction (UAR)** is an adverse reaction that is not consistent with the product information

A **suspected unexpected serious adverse reaction (SUSAR)** is any UAR that at any dose:

- results in death;
- is life threatening (i.e. the subject was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe);
- requires hospitalisation or prolongation of existing hospitalisation;
- results in persistent or significant disability or incapacity;
- is a congenital anomaly or birth defect.

11.2 Recording and Reporting

An SAE form must be used to record the details of the event and this will include a full description of the event, classification of the event using the above definitions, the PI's opinion on the causal relationship to the randomised management group and the timing of the event. All SAEs should be reported to the ICC within 24 hours or as soon as the event is recognised. The PI will be required to submit a follow up report to provide further information so that the outcome of the SAE can also be recorded. The PI is responsible for reporting the SAE to the IRB according to local guidelines.

A SUSAR form must be used to record the details of the event and this will include a full description of the event, classification of the event using the above definitions, the PI's opinion on the causal relationship to the suspected medicinal product, and the details of the suspected medicinal product. All SUSARs should be reported to the ICC within 24 hours or as soon as the event is recognised. The PI may be required to provide further details to supplement the initial SAE report and the outcome of the SUSAR will also need to be recorded. The PI is responsible for reporting the SUSAR to the IRB or regulatory administration according to local guidelines and regulatory requirements.

For China sites, apart from the above, all SAEs in relation to use of urapidil (Ebrantil) must also be reported in English by facsimile to Takeda Pharmacovigilance or designee: (i) Fatal and Life Threatening SAEs within 24 hours of the sponsor-investigator's observation or awareness of the event; and (ii) All other serious (non-fatal/non-life threatening) events within 4 calendar days of the sponsor-investigator's observation or awareness of the event.

11.3 Monitoring of SAEs

The ICC will closely monitor all SAEs for any relationship to the study procedures and protocol and clustering of events at a particular site. The protocol will be amended or the study will be stopped earlier if an excess of particular SAEs appear to be protocol related, for example severe hypotensive events requiring emergency treatment in the intensive BP lowering group. In addition, the ICC will submit all SAEs to the independent Data Safety Monitoring Board (DSMB) for review outside of the planned interim analysis meetings.

11.4 Monitoring of SUSARs

The ICC will closely monitor all SUSARs for any relationship to the study procedures and Protocol or clustering of events at a particular LCC. The ICC will submit all SUSARs to the independent DSMB for review outside of the planned interim analysis meetings. The ICC will also report all SUSARs to the MHRA and in addition will report to local regulatory authorities according to local requirements and guidelines.

12. QUALITY ASSURANCE

The study will be conducted at sites experienced in rtPA through established acute stroke unit thrombolysis programs. Regionally-based clinical research monitors will perform online and on-site data verification; and monitor conduct of the study, initially after the first few patients are randomised at a site and then at least once annually, according to patient recruitment numbers, whilst participating in the trial. *As ENCHANTED is an open trial of differing management strategies in a critical illness, monitoring serves to confirm that investigators are adhering to the protocol and Good Clinical Practice (GCP) Guidelines, and the accuracy of the data*. To ensure adherence to the study protocol, trained staff will undertake monitoring visits to confirm: (i) demographic and consent details of randomised patients; (ii) details of all SAEs against source documents; (iii) collect/correct outstanding/missing data; and (iv) check selected variables against source medical documents in a 10% random selection of patients.

12.1 Monitoring of Participating Centres

Prior to the initiation of the study at any participating centre, all designated research staff including the PI, Co-Investigator(s) and Research Nurse(s) will attend a training meeting on the study procedures. A study monitor, appointed by the ICC, will visit each participating centre to confirm there are adequate facilities and medical resources to conduct the study. In addition, all Investigators will be provided with materials detailing all study procedures. Before initiating the study, the PI and any Co-Investigators will provide up-to-date curriculum vitae (CV) in English to the ICC. The CVs of other designated research staff at the participating centre will be collected during the course of the study.

During the study, representatives of the ICC will visit all participating centres a minimum of twice in the recruitment phase of the study. The purpose of these visits will be to ensure that the study is conducted according to the protocol, ICH-GCP guidelines and meets relevant regional regulatory requirements. The monitor will verify relevant source documents according to a detailed monitoring plan available as a separate document.

At completion of the study, the monitor will ensure that there are plans in place for the long-term storage of all the relevant data and source documentation (for 15 years).

12.2 Auditing and Inspection by Government Regulatory Authorities

In addition, the study may also be audited by the third party and inspected by inspectors appointed by government regulatory authorities. CRFs, source documents and other study files must be accessible at all study sites at the time of auditing and inspection during the course of the study and after the completion of the study.

13. DATA MANAGEMENT

Randomisation and data entry will be performed at the participating centres via the password protected, internet based data management system (some centres may use a 24 hour telephone system for randomisation). This system, developed at the ICC includes reporting and data query management. Paper CRFs will be provided to centres, which prefer to use them for the initial data collection. All computerised forms will be electronically signed (via a unique password) by the authorised study staff and all changes made following the electronic signing will have an electronic audit trail with a signature and date. Centralised coding of outcomes will be performed by a trained medical coder.

14. STANDARDISATION OF OUTCOME ASSESSMENT

A Medical Review Committee (MRC) will review SAEs reported, brain imaging scans uploaded, and medical queries raised, in order to ensure that selected variables meet the same medical criteria. The MRC comprises experts in cerebrovascular disease. The brain imaging scans are analysed by Imaging Adjudication Committee (IAC) for any ICH. The adjudication of every scan is made without knowledge of which randomised group the patient was allocated. The IAC comprises expert clinical scientists. The members of the MRC and IAC are provided with explicit instructions and manuals detailing the criteria to be followed.

15. STATISTICAL CONSIDERATIONS

15.1 Sample size

*Arm **[A]** comparison of low- versus standard-dose rtPA* Based on pooled trials data in the Cochrane review of thrombolysis in AIS, the rate of death or disability (mRS score of 2-6) in patients who receive standard-dose i.v. rtPA is 50%.[7] Non-randomised studies suggest that low-dose rtPA provides similar clinical outcomes to the standard-dose rtPA (i.e. risk ratio 1.0).[22-24] For comparison between low- and standard-dose rtPA, a non-inferiority margin is based on the pooled Cochrane review of thrombolysis in AIS,[7] where the overall risk ratio of standard-dose rtPA versus control (placebo) with respect to death or disability was 0.76 (95%CI 0.66-0.87). Taking a conservative approach, as used in the Ongoing Telmisartan Alone and in Combination with Ramipril Global Endpoint Trial (ONTARGET),[55] the 40th percentile point around the risk reduction estimate (0.77) rather than the observed risk ratio has been chosen as a more robust reference to describe the effects of standard-dose rtPA, which can be translated into a margin of excess risk of placebo versus standard-dose rtPA of 1.29. As recommended by the United States Food and Drug Administration (FDA), the clinical margin representing the largest acceptable inferiority of the test to control is set at 50% (i.e. risk ratio 1.14) of the margin of the excess risk of 1.29. Thus, a *relative non-inferiority margin* of *14%* (i.e. risk ratio 1.14) provides assurance that low-dose rtPA retains at least half of the effects of standard-dose rtPA, provided the upper limit of the 95% CI of low- versus standard-dose rtPA is less than this non-inferiority margin. However, as there is potential for a negative interaction between intensive BP lowering and low-dose rtPA, the primary event rates will be 46.25% in patients who receive standard-dose rtPA and 46.75% in those who receive low-dose rtPA **(Table 6),** such that the *absolute non-inferiority margin rate* will be *6.5%* (relative non-inferiority margin of 14% x the primary event rate in standard-dose rtPA group of 46.75%). A sample size of 3300 (1650 per group) provided >90% power (1-sided α =0.025) to achieve the non-inferiority setting (assuming a 5% drop-out) with the ability also to make an assessment of the superiority of low- versus standard-dose rtPA. Arm [A] recruitment completed with 3310 patients in August 2015.

Table 6 Primary outcome event rates taking account of any interaction between treatment arms

	Standard-dose rtPA	Low-dose rtPA	AVERAGE
Guideline-based BP lowering	50.00%	50.00%	***50.00%***
Intensive BP lowering	42.50%	43.50%	***43.00%***
AVERAGE	***46.25%***	***46.75%***	

<u>*Arm **[B]** comparison of early intensive versus guideline-based BP lowering*</u> The SITS-ISTR registry[44] indicates a ≥15 mmHg systolic BP difference between randomised groups (i.e. 140-150 mmHg vs 180 mmHg systolic targets) is likely to be associated with ≥15% reduction in the outcome of death or disability in patients who receive standard-dose rtPA. However, assuming a potential interaction between low-dose rtPA and intensive BP lowering, a more conservative 13% reduction in outcome is expected in patients who receive low-dose rtPA in combination with intensive BP lowering. Assuming event rates of 50% in guideline-based BP lowering group and 43% in the intensive BP lowering group **(Table 6)**, a sample size of 2100 (1050 per group) will provide >80% power (2-sided α = 0.1) to detect 14% relative reductions in the primary outcome in the intensive BP lowering group, with 5% drop-out.

Table 7 Event rates for sICH taking account of potential interaction between 2 treatment arms

	Standard-dose rtPA	Low-dose rtPA	AVERAGE
Guideline-based BP lowering	7.00%	4.20%	***5.60%***
Intensive BP lowering	4.20%	2.69%	***3.44%***
AVERAGE	***5.60%***	***3.44%***	

Table 8 Event rates for any ICH taking account of potential interaction between 2 treatment arms

	Standard-dose rtPA	Low-dose rtPA	AVERAGE
Guideline-based BP lowering	23.00%	17.00%	***20.00%***
Intensive BP lowering	13.80%	10.90%	***12.30%***
AVERAGE	***18.40%***	***14.00%***	

<u>*Assessment of the secondary outcomes of sICH*</u> In the Cochrane review, the overall risk of sICH following standard-dose rtPA was 7%,[7] while registry studies have reported rates of 4-10% depending on definitions and other factors.[44,45] Observational studies of Japanese patients who have received low-dose i.v. rtPA suggest lower risks of sICH (3-4%, risk reduction >40%).[22-24] Based on the SITS-ISTR registry,[44] an expected 15 mmHg difference between randomised groups of BP lowering is likely to be associated with ≥40% reduction in sICH in those who receive standard-dose rtPA. Assuming a potential interaction between low-dose rtPA and intensive BP lowering, a more conservative 36% reduction is expected in patients who receive low-dose rtPA. Event rates are estimated to be 5.6% in patients who receive standard-dose rtPA and 3.44% in those who receive low-dose rtPA **(Table 7)**. The sample size of 3300 (1650 patients in each group) provided >80% power (2-sided α =0.05) to detect >40% relative reductions in sICH for the low-dose rtPA group with 5% of drop-out.

In the Cochrane review, the overall risk of any ICH following standard-dose rtPA was 23%.[7] Observational studies of Japanese patients who have received low-dose i.v. rtPA suggest lower risks of any ICH (17%, risk reduction 23%).[22-24] Based on the SITS-ISTR registry,[44] an expected 15 mmHg difference between randomised groups of BP lowering is likely to be associated with ≥40% reduction in any ICH in those who receive standard-dose rtPA. Assuming a potential interaction between low-dose rtPA and intensive BP lowering, a more conservative 36%

reduction is expected in patients who receive low-dose rtPA. With an average of 20% rate of any ICH among patients who receive guideline-based BP lowering and 12.30% among those with intensive BP lowering **(Table 8)**, the study will provide >90% power (2-sided α =0.05) to detect reductions in any ICH from intensive BP lowering, with 5% of drop out.

*In summary, a sample size of 3300 (1650 per group) for arm **[A]** (i.e. rtPA dose) provided >90% power to detect (i) non-inferiority (relative margin 14% [i.e. relative risk 1.14], absolute margin rate 6.5%) of low-dose rtPA on the primary outcome (one-sided α = 0.025), and (ii) ≥80% power to detect plausible 40% reductions in risks of sICH with low-dose rtPA, with 5% drop-out.* Arm [A] recruitment completed with 3310 patients in August 2015. *A sample size of 2100 (1050 per group) for arm **[B]** (i.e. BP lowering intensities) will provide ≥80% power to detect superiority of intensive BP lowering and any ICH (2-sided α =0.10) with 5% drop-out. Given overlap of 939 patients in the combined arms **[A]** and **[B]**, an expected total of 4500 patients will participate in the study.*

15.2 Statistical Analyses

In arm [B], the intention to treat principle will be applied in analyses. Baseline characteristics will be summarised by treatment group. For patients 'lost to final follow-up', data collected from randomisation to the time of last contact will be included in analyses. The primary end-point of functional recovery will be based upon a comparison of ordinal shift in scores on the mRS for superiority using ordinal logistic regression. The categorical secondary outcomes will be analysed by means of a chi-square test. Continuous endpoints will be summarised by means or medians, with the treatment effects tested by a Wilcoxon test that assumes skewed data. HRQoL EQ5D scores will be combined to provide an overall health utility score that will be calculated with population norms from the United Kingdom. The primary analysis will be unadjusted. Safety data will be tabulated using MedDRA terminology. Heterogeneity of treatment on the primary endpoint 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 systolic BP (above vs below median), NIHSS at baseline (above vs below median), final diagnosis of ischaemic stroke subtype, cerebral Infarction on CT scan, antiplatelet agent used, and evidence of atrial fibrillation. Analyses will be specified in detail in a full Statistical Analysis Plan. There are interim efficacy analyses planned after approximately 33% and 66% of the patients have been followed up at 90 days. The external DSMB will employ the Haybittle-Peto rule of an α <0.001 for any interim analyses finding in favour of a treatment to be considered significant. The DSMB will regularly monitor SAEs (i.e. deaths, sICH, and neurological deterioration), for which any excess would trigger discussions over stopping for harm. The α-level for the final analysis will be the conventional significance level (α = 0.10) given the infrequent interim analyses, their extremely low α levels, and the requirement for confirmation in subsequent analyses.

16. PUBLICATIONS AND REPORTS

Publication of the main reports from the study will be in the name of the Enhanced Control of Hypertension and Thrombolysis Stroke Trial (ENCHANTED) Investigators. Full editorial control will reside with a Writing Committee approved by the SC.

Investigators have the right to publish or present the results of the study. However, as this is a multi-site academic study, investigators agree not to publish or publicly present any interim results of the study without the prior written consent of the SC. Investigators further agree to provide the SC at least 30 days prior to submission for publication or presentation, review of copies of abstracts or manuscripts (including without limitation, text and PowerPoint presentation slides and any other texts of transmissions or media presentations) that report any results of the study.

The SC shall have the right to review and comment with respect to publications, abstracts, slides, and manuscripts. The SC also have the right to review and comment on the data analysis and presentation with regard to the accuracy of the information, the protection of the rights of individuals, and to ensure that the presentation is fairly balanced and in compliance with appropriate regulations.

If the parties disagree concerning the appropriateness of the data analysis and presentation, and/or confidentiality, the particular investigator(s) will agree to meet with members of the SC at the clinical site or as otherwise agreed, prior to submission for publication, for the purpose of making good faith efforts to discuss and resolve any disagreements.

Writing Committees will be formed from members of the various committees, statisticians, research fellows and investigators. They will prepare the main reports of the study to be published in the name of "ENCHANTED Investigators" with credit assigned to the collaborating investigators and other research staff. Presentations of the study findings will be made at national and international meetings concerned with the management of stroke, cardiovascular disease, and hypertension.

Authors of publications must meet the International Committee of Medical Journal Editors (ICMJE) guidelines for authorship that follow:

1 Authors must make substantial contributions to the conception and design of the trial, acquisition of data, or analysis of data and interpretation of results;

2 Authors must draft the publication or, during draft review, provide contributions (data analysis, interpretation, or other important intellectual content) leading to significant revision of the manuscript with agreement by the other authors;

3 Authors must provide approval of the final draft version of the manuscript before it is submitted to the journal for publication.

All contributors who do not meet the 3 criteria for authorship should be listed in an acknowledgments section within the publication, if allowed by the journal, per ICMJE guidelines for acknowledgement.

17. ORGANISATION

ENCHANTED is an academic initiated and conducted study to be managed by an ICC based at the George Institute for Global Health, University of Sydney, Australia. The study is overseen by an International Steering Committee comprised of world experts in the fields of stroke, hypertension, neurology, geriatrics, cardiovascular epidemiology and clinical trials. The ICC communicates with regional committees and approximately 100+ participating hospitals in Australia/New Zealand, Asia, Europe and South America. Sites will be administratively tied through a structure designed to enhance effective communication and collaboration as well as monitor and maintain operations through adherence to a common protocol. Central coordination is from The George Institute, Sydney; RCCs are located in Beijing, Ludhiana, Ho Chi Minh City, Leicester, Porto Alegre, and Santiago. The inclusion of focussed substudies, using CT/MRI diffusion perfusion and angiography, and TCD, for which separate funding will be sought, will advance the understanding of pathophysiological mechanisms of acute ischaemic stroke, the interpretation of the results of ENCHANTED, and inform clinical care and future studies.

17.1 Steering Committee (SC)

Responsibilities: Overall responsibility for the execution of the study design, protocol, data collection and analysis plan, as well as publications. The SC has the right to appoint new members and co-opt others to add to the integrity of the conduct of the study and analyses. Provisional list of SC is given below:

Professor Craig Anderson (Principal Investigator), The George Institute, University of Sydney, Australia

Professor John Chalmers (Chair), The George Institute, University of Sydney, Australia

Professor Richard Lindley, The George institute, University of Sydney, Australia

Professor Hisatomi Arima, Department of Preventive Medicine and Public Health, Faculty of Medicine, Fukuoka University, Fukuoka, Japan

Professor Jiguang Wang, Ruijin Hospital, Shanghai Jiaotong University School of Medicine, Shanghai, China

A/Prof Mark Parsons, John Hunter Hospital, Newcastle Neurosciences Institute, Australia

A/Prof Christopher Levi, John Hunter Hospital, Newcastle Neurosciences Institute, Australia

Professor Yining Huang, Peking University First Hospital, Peking

A/Professor Vijay K Sharma, National University Hospital, Singapore

Dr Nguyen Huy Thang, 115 The People Hospital, Ho Chi Minh City, Vietnam

Professor Jeyaraj D Pandian, Christian Medical College, Ludhiana, Punjab, India

Professor Jong Sung Kim, Asan University Hospital, Seoul, South Korea

Professor Christian Stapf, Neurologie Vasculaire, Hôpital Notre-Dame - Pavillon Deschamps and Université de Montréal Chercheur Régulier, Montreal, Canada

Professor Pablo Lavados, Clinica Alemana de Santiago, Universidad del Desarrollo and Universidad de Chile-Instituto de Neurocirugia, Santiago, Chile

Professor Tom Robinson, University of Leicester, United Kingdom

Professor Tsong-Hai Lee, Neurology Department, Linkou Chang Gung Memorial Hospital, Taoyuan, Taiwan

Professor Sheila Martins, Brazilian Stroke Network and Hospital de Clínicas de Porto Alegre, Brazil

Professor Octavio Pontes-Neto, Neurology Department, Ribeirão Preto School of Medicine, Brazil

Dr Shoichiro Sato, National Cerebral and Cardiovascular Center, Osaka, Japan

Professor Joanna Wardlaw, Centre for Clinical Brain Science, University of Edinburgh, Edinburgh, UK

17.2 International Coordinating Centre (ICC)

The ICC is at The George Institute for Global Health (GI), University of Sydney

Responsibilities: Day to day management of the study, data and project management, committee coordination, assistance with ethics committee applications, protocol and procedures training for participating centres, initiation visits to participating centres, monitoring of data quality and adherence to applicable guidelines and regulations, preparation of study data for analysis and publication.

17.3 Regional Coordinating Centres (RCC)

Responsibilities: Provide advice to the ICC on regional issues relevant to the set up and management of the study. In conjunction with the ICC, provide assistance and support and monitor study progress at regional participating centres, including data quality and adherence to the study protocol.

17.4 Imaging Adjudication Committee (Core Lab/Brain Imaging Analysis)

Responsibilities: To measure haemorrhagic complications (haematoma volume) and ischaemic/infarction on all de-identified and blinded brain imaging scans (blinded by allocation group and timing of scan).

17.5 Medical Review Committee

Responsibilities: To review SAEs reported, brain imaging scans uploaded and medical queries raised, in order to ensure that selected variables meet the same medical criteria.

17.6 Data Safety Monitoring Board (DSMB)

Responsibilities: Monitor blinded response variables and serious adverse events for early dramatic benefits or potential harmful effects using the approach developed by Sir Richard Peto for safety monitoring and provide reports to the ICC on recommendations to continue or temporarily halt recruitment to the study.
Members of the DSMB include:
Professor John Simes (Chair), University of Sydney, Sydney, (NSW) Australia;
Professor Peter Sandercock, University of Edinburgh, Edinburgh, Scotland;
Professor Graeme Hankey, Royal Perth Hospital, Perth, (WA) Australia;
Professor Marie-Germaine Bousser, Hôpital Lariboisière, Paris, France;
Professor KS Lawrence Wong, Prince of Wales Hospital, Chinese University of Hong Kong, Hong Kong.

A DSMB will review unblinded data from the study at regular intervals during follow-up, and will monitor BP separation (between the two groups), drop-out and event rates. Two interim efficacy analyses are planned after 30% and 60% of the patients have been followed up at 90 days. Prior to the first interim analysis a detailed Statistics Analysis Plan (SAP) will be completed and placed in the file. The SAP will contain a more comprehensive explanation than described herein of the methodology used in the statistical analyses, and in particular will specify the stopping rule used. The SAP will also contain the rules and data handling conventions used to perform the analyses, and the procedure used for accounting for missing data.

17.7 Participating Centres

Neurology Wards / Neuroscience Departments / Acute Stroke Units
Responsibilities: Overall management of study at own hospital in line with the study protocol; study nurse recruitment and orientation; protocol education of colleagues, patient recruitment, data collection and data transfer to the ICC, data query resolutions, liaison with local Hospital Research Ethics Committee/Institutional Review Board, adherence to local ethics guidelines and reporting requirements, adverse event reporting to local Hospital Research Ethics Committee/Institutional Review Board and to the ICC in accordance with protocol.

18. FUNDING

ENCHANTED is supported by two Project Grants from the NHMRC of Australia for the period 2012 to 2018. In addition, the Stroke Association of the United Kingdom provides two grants to support the study coordination in the United Kingdom for 5 years from 2012 to 2018; the

National Council for Scientific and Technological Development of Brazil supports the study in Brazil; the Ministry for Health, Welfare and Family Affairs of the Republic of Korea provided funding to support some coordination costs in Korea for Arm A of the study until 2015; Takeda China provides project grant support for the study only in China for the period 2016 to 2019. The funding allows for some monies to be provided to selected sites to subsidise the cost of rtPA used in participating patients in those sites with fee-for-service health care. *The funders of the study have no role in the study design, the collection, analysis or interpretation of the data, or in writing of reports.*

19. TIMELINES

Over 100 sites have expressed interest in participating, most in Asia (60 sites) Australia/New Zealand (12), Europe (60), and South America (30). The required total sample of 4800 patients ([50%] from Asia) being achieved over 6 years, with each site recruiting an average of 6 patients per year, appears realistic given that these sites treat 20-60 patients with rtPA for AIS annually. With extra time for developing the database and systems, employment and training of staff, ethics committee and regulatory approvals across multiple sites/countries (~12-24 months), and for 3-month follow-up and close-out periods, respectively, the total duration of the study was originally estimated at 5 years. However, recruitment was faster for the rtPA dose arm compared to the BP intensity arm of the study: the former completing recruitment of 3300+ patients whilst the latter recruited 1000+ patients, in August 2015. Recruitment in the BP intensity arm of the study, therefore, continues for the period 2016 to 2018, with presentation of the results planned for mid-2019.

	2011	2012	2013	2014	2015	2016	2017	2018	2019
Start-up phase (n=200)									
Expansion phase (n=1100)									
Main phase (n=3200)									
Close-out phase and analyses of rtPA dose arm									
Main results of rtPA dose arm presentation						X			
Ongoing recruitment into BP intensity arm									
Close-out phase and analyses of BP intensity arm									
Main results of BP intensity arm presentation									X

20. OUTCOMES AND SIGNIFICANCE

Stroke is a major global disease burden, for which the thrombolytic agent rtPA is the only proven medical treatment for AIS, yet used in only a minority of cases due to problems of access from low awareness of stroke symptoms, poor transport, limited expert care and diagnostic facilities, and the high cost of treatment in many parts of the world. As most strokes occur in the developing countries, only treatments that are low cost and widely applicable will have significant public health impact. Arm [A] of the study has shown that low-dose rtPA was not non-inferior to standard-dose rtPA according to the primary endpoint defined by the conventional binary cut-point analysis of the mRS; however, it was non-inferior according to the modern shift analysis of the full range of categories of the mRS. Moreover, low-dose rtPA produced significantly fewer sICH and early deaths. Since low-dose rtPA and early intensive BP lowering both fulfil this requirement, ENCHANTED could have a major impact in reducing the burden of stroke by providing evidence that could underpin access to cheaper, safer and effective treatments, used either alone and in combination, in the management of this condition. As a large sample size is required to establish effects on clinical meaningful outcomes, the research cannot be undertaken just within Australia; international collaboration is required to provide the first reliable evidence regarding the balance of benefits and risks of different doses of rtPA and intensities of BP lowering in acute ischaemic stroke. Given their applicability to millions of people with acute ischaemic stroke worldwide each year, the results will be published in prominent medical journals, presented at national and international meetings, incorporated into national clinical guidelines, and widely published in the media to further facilitate the rapid transfer into clinical practice.

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Appendix 1A - BP management protocol WITHOUT Labetalol

Early intensive BP lowering group	**TREATMENT PROTOCOL**
INITIAL therapy	
BP Target	**SBP 130-140 mmHg** reached within 60 minutes of Randomisation into the BP arm
Monitoring	• Continuous HR monitoring • Record BP/HR q 5 mins during <u>active</u> treatment, then q 15 min for first hour, q 30 min for next 5 hours and then hourly to 24 h
Hydralazine (IV)	• Hydralazine test dose: 5 mg IV bolus over 1 minute • If SBP >140 mmHg, repeat 5 mg IV bolus in 5 minutes • If SBP still > 140mmHg, give 10 mg IV bolus q 5 mins until target SBP reached • Increase to 20 mg bolus if required • Maximum hydralazine dose = 240mg
Metoprolol (IV)	If BP persistently > 140 mmHg: • ADD Metoprolol 5 mg IV bolus over 3-5 minutes, repeat 5mg bolus in 5 minutes x 2 if necessary but do NOT give if HR<55bpm
Glyceryl Trinitrate (topical)	If BP persistently > 140 mmHg: ADD topical glyceryl trinitrate (paste or patch) at a rate of 5-10 mg/24 hour (≈ 200-400 μg/hour). NB: also known as topical nitroglycerin
Continuous IV Infusions (requires ICU admission)	If BP persistently > 140 mmHg: • Start infusion of hydralazine - 50-150 μg/min • If target still not reached ADD infusion of glyceryl trinitrate 1-100 μg /min • OR start infusion of Nicardipine 5-15 mg/hour

MAINTENANCE therapy	
BP Target	Maintenance of SBP 130-140 mmHg
Monitoring	Once SBP is under target (confirmed by 4 readings 15 minutes apart): • Record BP/HR q 30 minutes for 5 hours and then q 1 h for 18 h
IV treatment prn	If SBP exceeds 140mmHg at any point: • Give Hydralazine 10-20 mg boluses. BP and HR should then be recorded 5 and 15 minutes after each bolus • If SBP is <140mmHg, give further Hydralazine 10-20 mg boluses (dependent on initial dose) q 6 hours for first 24 hours (total of 3 doses) • If SBP < 130 mmHg, cease therapy

Oral treatment	Start treatment by 24 hours (use nasogastric if required) • If not contraindicated and no other drug is specifically indicated, start combination therapy of ACEI + diuretics ± previous antihypertensives

Note: Monoamine oxidase inhibitors are not recommended with this BP lowering agent and phosphodiesterase inhibitors must not be used with GTN.

Key to abbreviations:

ACEI – Angiotensin converting enzyme inhibitor; BP – blood pressure; bpm – beats per minute; HR – heart rate; ICU – intensive care unit; q – every; prn – as required; μg/Kg/min – micrograms per kilogram per minute; μg/min – micrograms per minute.

Appendix 1B - BP management protocol for centres WITH labetalol

Early intensive BP lowering group	**TREATMENT PROTOCOL**
INITIAL therapy	
BP Target	**SBP 130-140 mmHg** reached within 60 minutes of Randomisation into the BP arm
Monitoring	• Continuous HR monitoring • Record BP/HR q 5 mins during <u>active</u> treatment, then q 15 min for first hour, q 30 min for next 5 hours and then hourly to 24 h
Labetalol (IV)	• Labetalol test dose: 10 mg IV bolus over 1 minute • If SBP > 140 mmHg and HR > 55 bpm, repeat 10 mg bolus in 5 minutes. • 20 mg IV push q 5 mins until target SBP reached (< 140mmHg) or HR <55 bpm; increase to 40 mg bolus if required • Maximum labetalol dose: 300 mg / 24 hours
Hydralazine (IV)	If BP persistently > 140 mmHg: • ADD Hydralazine with a test dose: 5 mg IV bolus over 1 minute • If SBP > 140 mmHg, repeat 5 mg IV bolus in 5 minutes • If SBP still >140mmHg, give 10 mg IV bolus q 5 mins until target SBP reached. Increase to 20 mg bolus if required • Maximum hydralazine dose = 240mg/24 hours
Glyceryl Trinitrate (Topical)	If BP persistently > 140 mmHg: • ADD topical glyceryl trinitrate (paste or patch) at a rate of 5-10 mg/24hour (≈200-400 μg/hour). NB: also known as topical nitroglycerin
Continuous IV Infusions (requires ICU admission)	If BP persistently > 140 mmHg: • Labetalol infusion 2-8 mg/min to a maximum of 300 mg/24 hours (consider this if response to labetalol boluses is adequate but brief) • If target still not reached, ADD infusion of hydralazine 50-150 μg/min OR glyceryl trinitrate 1-100 μg /min • OR start infusion of Nicardipine 5-15 mg/hour

MAINTENANCE therapy	
BP Target	Maintenance of SBP 130-140 mmHg
Monitoring	Once SBP is under target (confirmed by 4 readings 15 minutes apart): • Record BP/HR q 30 minutes for 5 hours and then q 1 h for 18 h
IV treatment prn	If SBP exceeds 140mmHg at any point: • Give Labetalol (20-40 mg) **and/or** hydralazine (10-20 mg) boluses. BP and HR should then be recorded 5 and 15 minutes later • If SBP is <140mmHg, Labetalol 10-40 mg (dose dependent on initial response) should be administered q 6 hours for the first 24 hours after symptom onset (total of 3 doses) • If SBP < 130 mmHg or HR < 55 bpm, then cease treatment.

	• Maximum labetalol dose: 300 mg/24 hours • **Note: labetalol and hydralazine may be used together during the maintenance phase**
Oral treatment	Start treatment by 24 hours (use nasogastric if required). • If not contraindicated and no other drug is specifically indicated, start combination therapy of ACEI + diuretics in addition to previous anti-hypertensives

Note: Monoamine oxidase inhibitors are not recommended with labetalol. Phosphodiesterase inhibitors must not be used with GTN.

Key to abbreviations: ACEI – Angiotensin converting enzyme inhibitor; BP – blood pressure; bpm – beats per minute; HR – heart rate; ICU – intensive care unit; q – every; prn – as required; μg/Kg/min – micrograms per kilogram per minute; μg/min – micrograms per minute.

Appendix 1C - BP protocol for centres with Urapidil (China)

Early intensive BP lowering group	TREATMENT PROTOCOL
INITIAL therapy	
BP Target	**SBP 130-140 mmHg** reached within 60 minutes of Randomisation into the BP arm
Monitoring	• Continuous HR monitoring • Record BP/HR q 5 mins during <u>active</u> treatment, then q 15 min for first hour, q 30 min for next 5 hours and then hourly to 24 h
Urapidil (IV)	• Urapidil test dose: 5 mg IV bolus over 1 minute • If SBP > 140 mmHg and HR >55 bpm, repeat 5 mg bolus in 5 minutes • 10-25 mg IV push q 5 mins until target SBP reached (< 140mmHg) or HR <55 bpm • **If HR increases by >15 bpm or is >90 bpm, add IV beta blocker**
Hydralazine (IV)	If BP persistently >140 mmHg: • ADD Hydralazine with a test dose: 5 mg IV bolus over 1 minute • If SBP > 140 mmHg, repeat 5 mg IV bolus in 5 minutes • If SBP still > 140mmHg, give 10 mg IV bolus q 5 mins until target SBP reached. Increase to 20 mg bolus if required • Maximum hydralazine dose = 240mg/24 hours
Glyceryl Trinitrate (Topical)	If BP persistently > 140 mmHg: • ADD topical glyceryl trinitrate (paste or patch) at a rate of 5-10 mg/24hour (≈200-400 μg/hour). NB: also known as topical nitroglycerin
Continuous IV Infusions (requires ICU admission)	If BP persistently >140 mmHg: **<u>NB: It is recognized that many sites will proceed directly to urapidil infusion following an initial bolus.</u>** • Urapidil infusion 5-30 mg/hour • If target still not reached, ADD infusion of hydralazine 50-150 μg/min OR glyceryl trinitrate 1-100 μg/min

MAINTENANCE therapy	
BP Target	Maintenance of SBP 130-140 mmHg
Monitoring	Once SBP is under target (confirmed by 4 readings 15 minutes apart): • Record BP/HR q 30 minutes for 5 hours and then q 1 h for 18 h.
IV treatment prn	If SBP exceeds 140mmHg at any point: • Give Urapidil (10-25 mg) **and/or** hydralazine (10-20 mg) boluses. BP and HR should then be recorded 5 and 15 minutes later • If SBP is <140mmHg, Urapidil 10-25 mg (dose dependent on initial response) should be administered q 6 hours for the first 24 hours after symptom onset (total of 3 doses)

	• If SBP < 130 mmHg or HR < 55 bpm, then cease treatment • **If HR increases by >15 bpm or is >90 bpm, add IV beta blocker** • Note: urapidil and hydralazine may be used together during the maintenance phase
Oral treatment	Start treatment by 24 hours (use nasogastric if required) • If not contraindicated and no other drug is specifically indicated, start combination therapy of ACEI + diuretics in addition to previous anti-hypertensives

Note: Monoamine oxidase inhibitors are not recommended with this BP lowering agent and phosphodiesterase inhibitors must not be used with GTN.

Key to abbreviations: ACEI – Angiotensin converting enzyme inhibitor; BP – blood pressure; bpm – beats per minute; HR – heart rate; ICU – intensive care unit; q – every; prn – as required; μg/Kg/min – micrograms per kilogram per minute; μg/min – micrograms per minute.

Appendix 1D - BP protocol for centres with Phentolamine (China)

Early intensive BP lowering group	**TREATMENT PROTOCOL**
INITIAL therapy	
BP Target	**SBP 130-140 mmHg** reached within 60 minutes of Randomisation into the BP arm
Monitoring	• Continuous HR monitoring • Record BP/HR q 5 mins during active treatment, then q 15 min for first hour, q 30 min for next 5 hours and then hourly to 24 h
Phentolamine (IV)	• Phentolamine test dose: 2.5 mg IV bolus over 1 minute • If SBP > 140 mmHg and HR >55 bpm, repeat 2.5 mg bolus in 5 minutes • 5 mg IV push q 5 mins until target SBP reached (130-140mmHg) or HR <55 bpm • **If HR increases by >15 bpm or is >90 bpm, add IV beta blocker**
Hydralazine (IV)	If BP persistently >140 mmHg: • ADD Hydralazine with a test dose: 5 mg IV bolus over 1 minute • If SBP > 140 mmHg, repeat 5 mg IV bolus in 5 minutes • If SBP still >140mmHg, give 10 mg IV bolus q 5 mins until target SBP reached. Increase to 20 mg bolus if required • Maximum hydralazine dose = 240mg/24 hours
Glyceryl Trinitrate (Topical)	If BP persistently >140 mmHg: • ADD topical glyceryl trinitrate (paste or patch) at a rate of 5-10 mg/24hour (≈200-400 μg/hour). NB: also known as topical nitroglycerin
Continuous IV Infusions (requires ICU admission)	If BP persistently >140 mmHg: • Phentolamine infusion 0.2-5 mg/minute • If target still not reached, ADD infusion of hydralazine 50-150 μg/min OR glyceryl trinitrate 1-100 μg /min

MAINTENANCE therapy	
BP Target	Maintenance of SBP 130-140 mmHg
Monitoring	Once SBP is under target (confirmed by 4 readings 15 minutes apart): • Record BP/HR q 30 minutes for 5 hours and then q 1 h for 18 h.
IV treatment prn	If SBP exceeds 140mmHg at any point: • Give Phentolamine (5 mg) **and/or** hydralazine (10-20 mg) boluses. BP and HR should then be recorded 5 and 15 minutes later • If SBP is <140mmHg, Phentolamine 5 mg (dose dependent on initial response) should be administered q 6 hours for the first 24 hours after symptom onset (total of 3 doses) • If SBP < 130 mmHg or HR <55 bpm, then cease treatment • **If HR increases by >15 bpm or is >90 bpm, add IV beta**

	blocker • Note: phentolamine and hydralazine may be used together during the maintenance phase
Oral treatment	Start treatment by 24 hours (use nasogastric if required) • If not contraindicated and no other drug is specifically indicated, start combination therapy of ACEI + diuretics in addition to previous anti-hypertensives

Note: Monoamine oxidase inhibitors are not recommended with this BP lowering agent and phosphodiesterase inhibitors must not be used with GTN.

Key to abbreviations: ACEI – Angiotensin converting enzyme inhibitor; BP – blood pressure; bpm – beats per minute; HR – heart rate; ICU – intensive care unit; q – every; prn – as required; μg/Kg/min – micrograms per kilogram per minute; μg/min – micrograms per minute.

Appendix 1E - Additional IV Medication for BP Use in China

The drugs listed in this Appendix are additional medications for BP lowering that can be used in China sites.

1. Suggested IV medication for BP lowering

1) Esmolol

Dosage and administration:

Bolus or infusion: It is recommended that an initial loading dose of 0.5 milligrams/kg body weight (500 micrograms/kg) infused over a one-minute duration, followed by a maintenance infusion of 0.05 milligrams/kg/min (50 micrograms/kg/min) for the next 4 minutes. If it is efficacious, the maintenance infusion may be continued at 0.05 mg/kg/min. If an adequate therapeutic effect is not observed, repeat the same loading dosage and follow with a maintenance infusion. The maintenance infusion may be continued at 0.05 mg/kg/min or increased step wise (e.g. 0.1 mg/kg/min, 0.15 mg/kg/min or a maximum of 0.2 mg/kg/min) with each step being maintained for 4 or more minutes. The maintenance infusion may be increased to a maximum of 0.3 mg/kg/min. Maintenance dosages above 200 μg/kg/min (0.2 mg/kg/min) have not been shown to have significantly increased benefits.

2) Enalaprilat

Dosage and administration:

Therapy should be individualised. For patients on diuretic therapy, the dosage of enalaprilat should be reduced. Dose in hypertension is 1.25 mg every six hours administered intravenously over a five minute period. Doses higher than 5 mg every six hours are not suggested.

2. IV medication for BP lowering which can also be used

1) Diltiazem

Dosage and administration:

An initial dose of 10 mg or 0.5 mg - 0.25 mg/kg body weight infused within 3 minutes can be used. Diltiazem should be diluted in normal or glucose solutions to a concentration of 1% before use. This dose can be repeated after 15 minutes. A maintenance infusion of 5 μg - 15 μg/kg/min is also permitted.

2) Nitroglyceride

Dosage and administration:

Nitroglyceride injection 10 mg is diluted in 0.9% normal solution 500 ml or 5% glucose solution 500 ml. The initial dose of nitroglyceride is 5 drops/min, and under close BP monitoring may increase by 5 drops/min every 3-5 minutes. If the dose of 20 drops/min is still not efficacious, 10 drops/min can be added every 3-5 minutes. Doses usually can be from 5 to 50 drops/min.

Note: Phosphodiesterase inhibitors must not be used with GTN.

3) Nimodipine

Dosage and administration:

Nimodipine 50 ml/50 mg should be put in a micro pump and infused in a constant speed 4 ml/hour, once a day. Usually it can be used for 5 to 14 days. Then, change to oral nimodipine. However, the BP lowering effect of oral nimodopine is not obvious.

4) Furosemide

Dosage and administration:

The usual initial dose of furosemide is 20-80 mg. If needed, the same dose can be repeated every 2 hours. The total dosage cannot be more than 1 g/d. If it is not effective, the dose should not be increased, to avoid renal toxicity.

Appendix 1F- BP protocol for centres with Clevidipine

Early intensive BP lowering group	**TREATMENT PROTOCOL**
INITIAL therapy	
BP Target	**SBP 130-140 mmHg** reached within 60 minutes of Randomisation into the BP arm
Monitoring	• Continuous HR monitoring • Record BP/HR q 2 mins during <u>active</u> treatment, then q 15 min for first hour, q 30 min for next 5 hours and then hourly to 24 h
Clevidipine (Continuous IV Infusion) *(requires ICU admission)*	• Clevidipine initiation dose: 2 mg/hour continuous IV for the first 1.5minuts • If SBP >140 mmHg, DOUBLE the dose every 2-10 minutes (4, 8, 16 and then 32 mg/hour) • Maximum dose = 32.0mg/hour
Hydralazine (IV)	If BP persistently >140 mmHg: • ADD Hydralazine with a test dose: 5 mg IV bolus over 1 minute • If SBP >140 mmHg, repeat 5 mg IV bolus in 5 minutes • If SBP still > 140mmHg, give 10 mg IV bolus q 5 mins until target SBP reached. Increase to 20 mg bolus if required • Maximum hydralazine dose = 240mg/24 hours
Glyceryl Trinitrate (Topical)	If BP persistently >140 mmHg: • ADD topical glyceryl trinitrate (paste or patch) at a rate of 5-10 mg/24hour (≈200-400 μg/hour). NB: also known as topical nitroglycerin
Continuous IV Infusions (requires ICU admission)	If BP persistently >140 mmHg: • ADD infusion of hydralazine 50-150 μg/min OR glyceryl trinitrate 1-100 μg /min
MAINTENANCE therapy	
BP Target	Maintenance of SBP 130-140 mmHg
Monitoring	Once SBP is under target (confirmed by 4 readings 15 minutes apart): • Record BP/HR q 30 minutes for 5 hours and then q 1 h for 18 h.
Continuous IV treatment prn	If SBP exceeds 140mmHg at any point: • DOUBLE the dose of Clevidipine every 2-10 minutes (4, 8, 16 and then maximum dose of 32 mg/hour) • If SBP is <140mmHg, Keep the dose of Clevidipine • If SBP < 130 mmHg or HR < 55 bpm, then HALVE the dose of Clevidipine every 2-10 minutes and then cease treatment • **If HR increases by >15 bpm or is >90 bpm, add IV beta blocker**
Oral treatment	Start treatment by 24 hours (use nasogastric if required) • If not contraindicated and no other drug is specifically indicated, start combination therapy of ACEI + diuretics in addition to previous anti-

	hypertensives	

Note: Monoamine oxidase inhibitors are not recommended with this BP lowering agent and phosphodiesterase inhibitors must not be used with GTN.

Key to abbreviations: ACEI – Angiotensin converting enzyme inhibitor; BP – blood pressure; bpm – beats per minute; HR – heart rate; ICU – intensive care unit; q – every; prn – as required; mg/hour – milligram per hour; μg/Kg/min – micrograms per kilogram per minute; μg/min – micrograms per minute.

Appendix 1G - BP protocol for centres with Nicardipine

Early intensive BP lowering group	**TREATMENT PROTOCOL**
INITIAL therapy	
BP Target	**SBP 130-140 mmHg** reached within 60 minutes of Randomisation into the BP arm
Monitoring	• Continuous HR monitoring • Record BP/HR q 2 mins during <u>active</u> treatment, then q 15 min for first hour, q 30 min for next 5 hours and then hourly to 24 h
Nicardipine (Continuous IV Infusion) *(requires ICU admission)*	• Nicardipine initiation dose: 5 mg/hour continuous IV for the first 15 minutes • If SBP >140 mmHg, increase the dose by 2.5 mg/hour every 15 minutes (7.5, 10, 12.5 and then 15 mg/hour) • Maximum dose = 15 mg/hour
Hydralazine (IV)	If BP persistently >140 mmHg: • ADD Hydralazine with a test dose: 5 mg IV bolus over 1 minute • If SBP >140 mmHg, repeat 5 mg IV bolus in 5 minutes • If SBP still > 140mmHg, give 10 mg IV bolus q 5 mins until target SBP reached. Increase to 20 mg bolus if required • Maximum hydralazine dose = 240mg/24 hours
Glyceryl Trinitrate (Topical)	If BP persistently >140 mmHg: • ADD topical glyceryl trinitrate (paste or patch) at a rate of 5-10 mg/24hour (≈200-400 μg/hour). NB: also known as topical nitroglycerin
Continuous IV Infusions (requires ICU admission)	If BP persistently >140 mmHg: • ADD infusion of hydralazine 50-150 μg/min OR glyceryl trinitrate 1-100 μg /min

MAINTENANCE therapy	
BP Target	Maintenance of SBP 130-140 mmHg
Monitoring	Once SBP is under target (confirmed by 4 readings 15 minutes apart): • Record BP/HR q 30 minutes for 5 hours and then q 1 h for 18 h.
Continuous IV treatment prn	If SBP exceeds 140mmHg at any point: • INCREASE the dose of Nicardipine by 2.5 mg/hour every 15 minutes (7.5, 10, 12.5 and then 15 mg/hour) • If SBP is <140mmHg, Keep the dose of Nicardipine • If SBP < 130 mmHg or HR < 55 bpm, then DECREASE the dose of Nicardipine by 2.5mg/hour every 2-15 minutes and then cease treatment • **If HR increases by >15 bpm or is >90 bpm, add IV beta blocker**

Oral treatment	Start treatment by 24 hours (use nasogastric if required) • If not contraindicated and no other drug is specifically indicated, start combination therapy of ACEI + diuretics in addition to previous anti-hypertensives

Note: Monoamine oxidase inhibitors are not recommended with this BP lowering agent and phosphodiesterase inhibitors must not be used with GTN.

Key to abbreviations: ACEI – Angiotensin converting enzyme inhibitor; BP – blood pressure; bpm – beats per minute; HR – heart rate; ICU – intensive care unit; q – every; prn – as required; mg/hour – milligram per hour; μg/Kg/min – micrograms per kilogram per minute; μg/min – micrograms per minute.

Appendix 1H - BP protocol for centres with Nicardipine (Vietnam)

Early intensive BP lowering group	**TREATMENT PROTOCOL**
INITIAL therapy	
Indication	**SBP > 140 mmHg, then at least 2 times, 5 min apart**
BP Target	**SBP < 140mmHg** reached within 60 minutes of Randomisation into the BP arm
Monitoring	• Continuous HR monitoring • Record BP/HR q 5 mins during <u>active</u> treatment, then q 15 min for first hour, q 30 min for next 5 hours , then hourly for next 18h to 24 h (totally for initial 24h), and then every 3h in next 72h
Medication	
Nicardipine (Continuous IV Infusion) *(requires ICU admission)*	• Nicardipine initiation dose: 5 mg/hour continuous IV for the first 15 minutes • If SBP >140 mmHg, increase the dose by 1-2.5 mg/hour every 5 minutes (7.5, 10, 12.5 and then 15 mg/hour) • Maximum dose = 15 mg/hour
Nitroglycerin	If SBP > 140 mmHg after treatment maximum dose of Nicardipine Nitroglycerin dose: 1 – 100 µg /min

MAINTENANCE therapy	
BP Target	Maintenance of SBP 130-140 mmHg/72h
Monitoring	Once SBP is under target (confirmed by 4 readings 15 minutes apart): • Record BP/HR q 30 minutes for 5 hours and then q 1 h for 18 h.
Continuous IV treatment prn	IV infusion according to BP level, increasing or decreasing doses depends on BP stability. If SBP exceeds 140mmHg at any point: • INCREASE the dose of Nicardipine by 2.5 - 5 mg/2 – 5 minutes • If no reaching SBP target, increase IV infusion maintenance doses (amend 1 – 2.5 mg for each dose increase (e.g if maintenance dose of 2.5 mg/h, dose increased will be 3 – 4.5 mg/h) • If SBP is <140mmHg, Keep the dose of Nicardipine • If SBP < 130 mmHg or HR < 55 bpm: Cease treatment then if SBP≥140 mmHg, repeat the Nicardipine IV infusion with a half of the Dose before ceasing treatment. If SBP still >140 mmHg at maximum dose of Nicardipine, Nitroglycerine is able to be amended.

Oral treatment	When the BP is stable in 4 consecutive recording times (starting at the 20^{th} hour), oral medications are able to be used. • The patient using BP medication before stroke: previous anti-hypertensives can be used or switch to new suitable anti-hypertensives starting with a half of the dose which was used before stroke • Patient with no BP medication before stroke: ACEI is prioritized and/or combination therapy of ACEI + diuretics by increasing diuretics prn from low dose. • Monitoring HR and BP every 3 hrs to 72h

Note: Monoamine oxidase inhibitors are not recommended with this BP lowering agent and phosphodiesterase inhibitors must not be used with GTN.

Key to abbreviations: ACEI – Angiotensin converting enzyme inhibitor; BP – blood pressure; bpm – beats per minute; HR – heart rate; ICU – intensive care unit; q – every; prn – as required; mg/hour – milligram per hour; μg/Kg/min – micrograms per kilogram per minute; μg/min – micrograms per minute.

Appendix 1I - Current guideline –based BP management

RANDOMISED GROUP	TREATMENT
CONTROL GUIDELINE-BASED BP MANAGEMENT	**Use acute intravenous therapy ONLY IF SBP >180 mmHg** Oral anti-hypertensives and / or topical nitrates can be used when patient medically stable, as assessed by responsible clinician. Oral treatment should be started by discharge / transfer (**use nasogastric if required**). • If not contraindicated and no other drug is specifically required, start combination therapy ACEI + diuretic therapy in addition to previous anti-hypertensives

Key to abbreviations:
ACEI – Angiotensin converting enzyme inhibitor; SBP – systolic blood pressure.

Appendix 2 - Imaging protocol

It would be desirable to use the same modality for both pre-randomisation and follow-up imaging from the same subject. However if for technical or practical reasons this is not possible, mixed CT and MR acquisitions (eg CT pre-randomisation and MR follow-up) are acceptable.

CT scans should cover the entire brain from the foramen magnum to the vertex with 4–5 mm thick slices through the posterior fossa and 8–10 mm thick for the cerebral hemispheres, with no slice gap. Scans should be windowed on a width of 80 Hounsfield Units (HU) and a centre level of 35–40 HU. All patients (irrespective of treatment allocation) should have a follow-up scan at 24 hours. In addition a repeat scan is required if the patient deteriorates neurologically or ICH is suspected for any reason.

In addition to the diffusion/perfusion MRI or perfusion CT series, any structural MRI (GRE, T2, FLAIR) orCT (spiral CT, etc) sequences acquired at the same time should be included. For CT, spiral CT is to be preferred over CT MPR data or sequential axial CT acquisitions with thick slices. Suggested acquisition parameters are given in Table A1- A4 below.

If angiography (either MR or CT) have also been acquired, these should be submitted as well. Suggested acquisition parameters are given in Table A5 below.

Table A1.Recommended Acquisition Protocol for Perfusion-CT (PCT)

Acquisition Rate	1 image per second, (ideally at one source rotation per second
Total Acquisition Time Base Line Period	40 to 60 seconds 5-10 volumes should be acquired prior to contrast arrival
Kvp and	80 kVp (not 120 kVp)
mAs	100 mAs or higher
Contrast Volume	35-50 mL (with saline flush)
Delivery Rate	4-6 mL per second
Coverage	As dictated by configuration of hardware

Table A2.Recommended Acquisition Protocols for Perfusion-Weighted (PWI) MR Imaging

Sequence	Single-shot gradient-echo echoplanar imaging
TR	TR = 1500 to 2000 ms
TE	TE=35 to 45 ms @ 1.5T TE=25 to 30 ms @ 3T
Flip angle	flip angle =60 to 90° @ 1.5T, 60° @ 3.0T
Baseline	At least 10-12 Baseline images (please note the first few images prior to steady state are discarded)
Coverage	At least 12 slices, with same slice thickness and gap as DWI, increase TR and slice gap to achieve reasonable coverage.

Table A3. Recommended Acquisition Protocols for Diffusion-Weighted (DWI) MR Imaging

Sequence	Single-shot spin-echo echoplanar imaging
TR	Should be at least 4000 ms (but can be larger)
TE	Minimum achievable
Diffusion weighting (b values)	b=0 and 1000 sec/mm2
Coverage	At least 10-12 slices, with same slice thickness and gap as PWI.

Table A4 Example Acquisition Protocol for Spiral CT

Kvp	120
mAs	310
slice collimation	0.75 mm
pitch	0.65
Gantry Rotation	Maximum
Table feed speed	less than 7.5mm per gantry rotation

Table A5. Recommended Acquisition Protocol for CT angiography (CTA) and MR angiography (MRA)

CTA	
Kvp	100
mAs	120
Contrast (volume/type/rate)	50ml Omnipaque 300 at 4ml/sec
Flush (volume/type/rate)	40ml saline at 4ml/sec
delay	15secs
coverage	circle of Willis (upwards)
slice collimation	0.75mm
pitch	1.25

MRA	
Sequence	3D TOF 2 slab HR
TR (ms)	23
TE (ms)	2.7
Flip angle	20°
Locs / slab	32
Slice thickness	1.6
Slice gap	0
Matrix	320 x 224
ΦFOV	1
FOV	16
Slice orient	Straight axial
T-scan	5:46

Brain imaging (CTscan and/or MRI) must be uploaded to the ENCHANTED server to be analysed centrally for measurement of ischaemic lesion, measurement of areas of penumbra, sites of vessel occlusion, and haemorrhagic complications. The LCC will keep a hard copy in an uncompressed DICOM format onto a CD-ROM for site monitoring verification.

Brain images are only to be removed from the scanner server after confirmation of receipt of images has been sent to the study centre.

Appendix 3 - Health Scales

Glasgow Coma Scale (GCS)

Assessment	**Measure**	**Score**
Eye opening (E)	4= Spontaneous 3= To sound 2= To pain 1= Never	
Verbal response (V)	5= Oriented 4= Confused conversation 3= Inappropriate words 2= Incomprehensible sounds 1= None	
Motor response (M)	6= Obeys command 5= Localises pain 4= Withdrawal flexion 3= Abnormal flexion 2= Extension 1= None	
TOTAL		**……. / 15** (E + M + V)

NB. If the patient is intubated the verbal response should be scored 1.

When scoring the motor response, assess the response for the extremities of side unaffected by partial or complete paralysis.

NIH Stroke scale (National Institute of Health Stroke Scale)

Assessment	Response	Score
1a. Level of Consciousness: The investigator must choose a response, even if a full evaluation is prevented by such obstacles as an endotracheal tube, language barrier, orotracheal trauma/bandages. A 3 is scored only if the patient makes no movement (other than reflexive posturing) in response to noxious stimulation.	0 = Alert; keenly responsive. 1 = Not alert, but arousable by minor stimulation to obey, answer, or respond. 2 = Not alert, requires repeated stimulation to attend, or is obtunded and requires strong or painful stimulation to make movements (not stereotyped). 3 = Responds only with reflex motor or autonomic effects or totally unresponsive, flaccid, areflexic.	
1b. LOC Questions: The patient is asked the month and his/her age. The answer must be correct - there is no partial credit for being close. Aphasic and stuporous patients who do not comprehend the questions will score 2. Patients unable to speak because of endotracheal intubation, orotracheal trauma, severe dysarthria from any cause, language barrier or any other problem not secondary to aphasia are given a 1. It is important that only the initial answer be graded and that the examiner not "help" the patient with verbal or non-verbal cues.	0 = Answers both questions correctly. 1 = Answers one question correctly. 2 = Answers neither question correctly.	
1c. LOC Commands: The patient is asked to open and close the eyes and then to grip and release the non-paretic hand. Substitute another one step command if the hands cannot be used. Credit is given if an unequivocal attempt is made but not completed due to weakness. If the patient does not respond to command, the task should be demonstrated to them (pantomime) and score the result (i.e., follows none, one or two commands). Patients with trauma, amputation, or other physical impediments should be given suitable one-step commands. Only the first attempt is scored.	0 = Performs both tasks correctly. 1 = Performs one task correctly. 2 = Performs neither task correctly.	
2. Best Gaze: Only horizontal eye movements will be tested. Voluntary or reflexive (oculocephalic) eye movements will be scored but caloric testing is not done. If the patient has a conjugate deviation of	0 = Normal. 1 = Partial gaze palsy. This score is given when gaze is abnormal in one or both eyes, but where forced deviation or total gaze paresis are not present. 2 = Forced deviation, or total gaze paresis not	

Assessment	Response	Score
the eyes that can be overcome by voluntary or reflexive activity, the score will be 1. If a patient has an isolated peripheral nerve paresis (CN III, IV or VI) score a 1. Gaze is testable in all aphasic patients. Patients with ocular trauma, bandages, pre-existing blindness or other disorder of visual acuity or fields should be tested with reflexive movements and a choice made by the investigator. Establishing eye contact and then moving about the patient from side to side will occasionally clarify the presence of a partial gaze palsy.	overcome by the oculocephalic maneuver.	
3. Visual: Visual fields (upper and lower quadrants) are tested by confrontation, using finger counting or visual threat as appropriate. Patient must be encouraged, but if they look at the side of the moving fingers appropriately, this can be scored as normal. If there is unilateral blindness or enucleation, visual fields in the remaining eye are scored. Score 1 only if a clear-cut asymmetry, including quadrantanopia is found. If patient is blind from any cause score 3. Double simultaneous stimulation is performed at this point. If there is extinction patient receives a 1 and the results are used to answer question 11.	0 = No visual loss. 1 = Partial hemianopia. 2 = Complete hemianopia. 3 = Bilateral hemianopia (blind including cortical blindness).	
4. Facial Palsy: Ask, or use pantomime to encourage the patient to show teeth or raise eyebrows and close eyes. Score symmetry of grimace in response to noxious stimuli in the poorly responsive or non-comprehending patient. If facial trauma/bandages, orotracheal tube, tape or other physical barrier obscures the face, these should be removed to the extent possible.	0 = Normal symmetrical movement. 1 = Minor paralysis (flattened nasolabial fold, asymmetry on smiling). 2 = Partial paralysis (total or near total paralysis of lower face). 3 = Complete paralysis of one or both sides (absence of facial movement in the upper and lower face).	

Assessment	Response	Score
5 & 6. Motor Arm and Leg: The limb is placed in the appropriate position: extend the arms (palms down) 90 degrees (if sitting) or 45 degrees (if supine) and the leg 30 degrees (always tested supine). Drift is scored if the arm falls before 10 seconds or the leg before 5 seconds. The aphasic patient is encouraged using urgency in the voice and pantomime but not noxious stimulation. Each limb is tested in turn, beginning with the non-paretic arm. Only in the case of amputation or joint fusion at the shoulder or hip may the score be "9" and the examiner must clearly write the explanation for scoring as a "9".	0 = No drift, limb holds 90 (or 45) degrees for full 10 seconds. 1 = Drift, Limb holds 90 (or 45) degrees, but drifts down before full 10 seconds; does not hit bed or other support. 2 = Some effort against gravity, limb cannot get to or maintain (if cued) 90 (or 45) degrees, drifts down to bed, but has some effort against gravity. 3 = No effort against gravity, limb falls. 4 = No movement 9 = Amputation, joint fusion explain:	-
	5a. Left Arm	
	5b. Right Arm	
	0 = No drift, leg holds 30 degrees position for full 5 seconds. 1 = Drift, leg falls by the end of the 5 second period but does not hit bed. 2 = Some effort against gravity; leg falls to bed by 5 seconds, but has some effort against gravity. 3 = No effort against gravity, leg falls to bed immediately. 4 = No movement. 9 = Amputation, joint fusion explain:	-
	6a. Left Leg	
	6b. Right Leg	
7. Limb Ataxia: This item is aimed at finding evidence of a unilateral cerebellar lesion. Test with eyes open. In case of visual defect, insure testing is done in intact visual field. The finger-nose-finger and heel-shin tests are performed on both sides, and ataxia is scored only if present out of proportion to weakness. Ataxia is absent in the patient who cannot understand or is paralyzed. Only in the case of amputation or joint fusion may the item be scored "9", and the examiner must clearly write the explanation for not scoring. In case of blindness test by touching nose from extended arm position.	0 = Absent . 1 = Present in one limb . 2 = Present in two limbs If present, is ataxia in?	
	Right arm 1 = Yes 2 = No 9 = amputation or joint fusion, explain: ________________	-
	Left arm 1 = Yes 2 = No 9 = amputation or joint fusion, explain : ________________	-
	Right leg 1 = Yes 2 = No 9 = amputation or joint fusion, explain: ________________	-
	Left leg 1 = Yes 2 = No 9 = amputation or joint fusion, explain: ________________	-

Assessment	Response	Score
8. Sensory: Sensation or grimace to pin prick when tested, or withdrawal from noxious stimulus in the obtunded or aphasic patient. Only sensory loss attributed to stroke is scored as abnormal and the examiner should test as many body areas [arms (not hands), legs, trunk, face] as needed to accurately check for hemisensory loss. A score of 2, "severe or total," should only be given when a severe or total loss of sensation can be clearly demonstrated. Stuporous and aphasic patients will therefore probably score 1 or 0. The patient with brain stem stroke who has bilateral loss of sensation is scored 2. If the patient does not respond and is quadriplegic score 2. Patients in coma (item 1a=3) are arbitrarily given a 2 on this item.	0 = Normal; no sensory loss. 1 = Mild to moderate sensory loss; patient feels pinprick is less sharp or is dull on the affected side; or there is a loss of superficial pain with pinprick but patient is aware he/she is being touched. 2 = Severe to total sensory loss; patient is not aware of being touched in the face, arm, and leg.	
9. Best Language: A great deal of information about comprehension will be obtained during the preceding sections of the examination. The patient is asked to describe what is happening in the attached picture, to name the items on the attached naming sheet, and to read from the attached list of sentences. Comprehension is judged from responses here as well as to all of the commands in the preceding general neurological exam. If visual loss interferes with the tests, ask the patient to identify objects placed in the hand, repeat, and produce speech. The intubated patient should be asked to write. The patient in coma (question 1a=3) will arbitrarily score 3 on this item. The examiner must choose a score in the patient with stupor or limited cooperation but a score of 3 should be used only if the patient is mute and follows no one step commands.	0 = No aphasia, normal. 1 = Mild to moderate aphasia; some obvious loss of fluency or facility of comprehension, without significant limitation on ideas expressed or form of expression. Reduction of speech and/or comprehension, however, makes conversation about provided material difficult or impossible. For example in conversation about provided materials examiner can identify picture or naming card from patient's response. 2 = Severe aphasia; all communication is through fragmentary expression; great need for inference, questioning, and guessing by the listener. Range of information that can be exchanged is limited; listener carries burden of communication. Examiner cannot identify materials provided from patient response. 3 = Mute, global aphasia; no usable speech or auditory comprehension.	
10. Dysarthria: If patient is thought to be normal an adequate sample of speech must be obtained by asking patient to read or repeat words from the attached list. If the	0 = Normal. 1 = Mild to moderate; patient slurs at least some words and, at worst, can be understood with some difficulty. 2 = Severe; patient's speech is so slurred as to be	

Assessment	Response	Score
patient has severe aphasia, the clarity of articulation of spontaneous speech can be rated. Only if the patient is intubated or has other physical barrier to producing speech, may the item be scored "9", and the examiner must clearly write an explanation for not scoring. Do not tell the patient why he/she is being tested.	unintelligible in the absence of or out of proportion to any dysphasia, or is mute/anarthric. 9 = Intubated or other physical barrier, explain: _________________	
11. Extinction and Inattention (formerly Neglect): Sufficient information to identify neglect may be obtained during the prior testing. If the patient has a severe visual loss preventing visual double simultaneous stimulation, and the cutaneous stimuli are normal, the score is normal. If the patient has aphasia but does appear to attend to both sides, the score is normal. The presence of visual spatial neglect or anosagnosia may also be taken as evidence of abnormality. Since the abnormality is scored only if present, the item is never untestable.	0 = No abnormality. 1 = Visual, tactile, auditory, spatial, or personal inattention or extinction to bilateral simultaneous stimulation in one of the sensory modalities. 2 = Profound hemi-inattention or hemi-inattention to more than one modality. Does not recognize own hand or orients to only one side of space.	
TOTAL		/
Additional item, not a part of the NIH Stroke Scale score.		-
A. Distal Motor Function: The patient's hand is held up at the forearm by the examiner and patient is asked to extend his/her fingers as much as possible. If the patient can't or doesn't extend the fingers the examiner places the fingers in full extension and observes for any flexion movement for 5 seconds. The patient's first attempts only are graded. Repetition of the instructions or of the testing is prohibited.	0 = Normal (No flexion after 5 seconds). 1 = At least some extension after 5 seconds, but not fully extended. Any movement of the fingers which is not command is not scored. 2 = No voluntary extension after 5 seconds. Movements of the fingers at another time are not scored.	-
	a. Left Arm	
	b. Right Arm	

Modified Rankin Scale (mRS)

		Score
0 =	No symptoms at all.	
1 =	No significant disability despite symptoms, 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.	
		/ 6

European Quality Of Life (EuroQOL)

		Numbers
1.	Mobility	1= I have no problems in walking about 2= I have some problems in walking about 3= I am confined to bed
2.	Self-care	1= I have no problems with self-care 2= I have some problems washing or dressing myself 3= I am unable to wash or dress myself
3.	Usual activities (e.g. work, study, housework, family, or leisure activities)	1= I have no problems with performing my usual activities 2= I have some problems with performing my usual activities 3= I am unable to perform my usual activities
4.	Pain/ discomfort	1= I have no pain or discomfort 2= I have moderate pain or discomfort 3= I have extreme pain or discomfort
5.	Anxiety/ depression	1= I am not anxious or depressed 2= I am moderately anxious or depressed 3= I am extremely anxious or depressed

Appendix 4 - Standard acute care protocol

Airway Management:

Objectives: Normal SpO2 (≥ 92%)

- Monitor oxygen saturation continuously
- Oxygen supplementation is recommended only if patients de-saturate
- Intubate patients, who are unable to protect their airway, due to decreased level of consciousness and / or hypoxia / hypercarbia (pO2 <60 mm Hg or pCO2 >50 mm Hg)

Fluid Management:

Objectives: Isovolaemia with an isotonic solution; avoid hypokalemia

- Isotonic intravenous therapy, avoid hypotonic solutions
- Rate to be determined by oral/nasogastric intake
- Consider potassium supplementation if therapy is prolonged

Body Temperature:

Objectives: Maintain normothermia

- Monitor body temperature 4 times a day
- Investigate for infectious cause of any fevers
- Treat all fevers with paracetamol and / or cooling fans / blankets

Diet:

Objectives: Avoidance of aspiration, maintenance of nutrition, avoidance of ulcers

- Patients with dysphagia or suspected dysphagia should be kept nil by mouth until a formal swallowing assessment can be performed
- Alternative diets may be required, i.e. thickened fluids/diced
- Nasogastric feeding is recommended for patients who remain obtunded or severely dysphagic >24 hours
- Consider cytoprotective agents (proton pump inhibitor or H-2 antagonist)

Activity:

Objectives: Mobilize safely, avoid complications of immobility

- Patients should be mobilized only with supervision
- Delay mobilization in patients where elevated ICP is suspected
- Start physiotherapy as soon as patient is medically stable

DVT Prophylaxis:

Objectives: Avoid deep venous thrombosis / pulmonary embolism

- Compression stockings or pneumatic devices are recommended immediately
- Consider prophylactic sub-cutaneous heparinoids in patients with poor mobilization

Appendix 5 - Declaration of Helsinki

Appendix 5 - Declaration of Helsinki

WORLD MEDICAL ASSOCIATION DECLARATION OF HELSINKI
Ethical Principles for Medical Research Involving Human Subjects

Adopted by the 18th WMA General Assembly, Helsinki, Finland, June 1964
and amended by the:
29th WMA General Assembly, Tokyo, Japan, October 1975
35th WMA General Assembly, Venice, Italy, October 1983
41st WMA General Assembly, Hong Kong, September 1989
48th WMA General Assembly, Somerset West, Republic of South Africa, October 1996
52nd WMA General Assembly, Edinburgh, Scotland, October 2000
53rd WMA General Assembly, Washington DC, USA, October 2002 (Note of Clarification added)
55th WMA General Assembly, Tokyo, Japan, October 2004 (Note of Clarification added)
59th WMA General Assembly, Seoul, Republic of Korea, October 2008
64th WMA General Assembly, Fortaleza, Brazil, October 2013

Preamble

1. The World Medical Association (WMA) has developed the Declaration of Helsinki as a statement of ethical principles for medical research involving human subjects, including research on identifiable human material and data.

   The Declaration is intended to be read as a whole and each of its constituent paragraphs should be applied with consideration of all other relevant paragraphs.

2. Consistent with the mandate of the WMA, the Declaration is addressed primarily to physicians. The WMA encourages others who are involved in medical research involving human subjects to adopt these principles.

General Principles

3. The Declaration of Geneva of the WMA binds the physician with the words, “The health of my patient will be my first consideration,” and the International Code of Medical Ethics declares that, “A physician shall act in the patient's best interest when providing medical care.”

4. It is the duty of the physician to promote and safeguard the health, well-being and rights of patients, including those who are involved in medical research. The physician's knowledge and conscience are dedicated to the fulfilment of this duty.

5. Medical progress is based on research that ultimately must include studies involving human subjects.

6. The primary purpose of medical research involving human subjects is to understand the causes, development and effects of diseases and improve preventive, diagnostic and therapeutic interventions (methods, procedures and treatments). Even the best proven interventions must be evaluated continually through research for their safety, effectiveness, efficiency, accessibility and quality.

7. Medical research is subject to ethical standards that promote and ensure respect for all human subjects and protect their health and rights.

8. While the primary purpose of medical research is to generate new knowledge, this goal can never take precedence over the rights and interests of individual research subjects.

9. It is the duty of physicians who are involved in medical research to protect the life, health, dignity, integrity, right to self-determination, privacy, and confidentiality of personal information of research subjects. The responsibility for the protection of research subjects must always rest with the physician or other health care professionals and never with the research subjects, even though they have given consent.

10. Physicians must consider the ethical, legal and regulatory norms and standards for research involving human subjects in their own countries as well as applicable international norms and standards. No national or international ethical, legal or regulatory requirement should reduce or eliminate any of the protections for research subjects set forth in this Declaration.

11. Medical research should be conducted in a manner that minimises possible harm to the environment.

12. Medical research involving human subjects must be conducted only by individuals with the appropriate ethics and scientific education, training and qualifications. Research on patients or healthy volunteers requires the supervision of a competent and appropriately qualified physician or other health care professional.

13. Groups that are underrepresented in medical research should be provided appropriate access to participation in research.

14. Physicians who combine medical research with medical care should involve their patients in research only to the extent that this is justified by its potential preventive, diagnostic or therapeutic value and if the physician has good reason to believe that participation in the research study will not adversely affect the health of the patients who serve as research subjects.

15. Appropriate compensation and treatment for subjects who are harmed as a result of participating in research must be ensured.

Risks, Burdens and Benefits

16. In medical practice and in medical research, most interventions involve risks and burdens.

    Medical research involving human subjects may only be conducted if the importance of the objective outweighs the risks and burdens to the research subjects.

17. All medical research involving human subjects must be preceded by careful assessment of predictable risks and burdens to the individuals and groups involved in the research in comparison with foreseeable benefits to them and to other individuals or groups affected by the condition under investigation.

    Measures to minimise the risks must be implemented. The risks must be continuously monitored, assessed and documented by the researcher.

18. Physicians may not be involved in a research study involving human subjects unless they are confident that the risks have been adequately assessed and can be satisfactorily managed.

    When the risks are found to outweigh the potential benefits or when there is conclusive proof of definitive outcomes, physicians must assess whether to continue, modify or immediately stop the study.

19. Some groups and individuals are particularly vulnerable and may have an increased likelihood of being wronged or of incurring additional harm.

    All vulnerable groups and individuals should receive specifically considered protection.

20. Medical research with a vulnerable group is only justified if the research is responsive to the health needs or priorities of this group and the research cannot be carried out in a non-vulnerable group. In addition, this group should stand to benefit from the knowledge, practices or interventions that result from the research.

Scientific Requirements and Research Protocols

21. Medical research involving human subjects must conform to generally accepted scientific principles, be based on a thorough knowledge of the scientific literature, other relevant sources of information, and adequate laboratory and, as appropriate, animal experimentation. The welfare of animals used for research must be respected.

22. The design and performance of each research study involving human subjects must be clearly described and justified in a research protocol.

    The protocol should contain a statement of the ethical considerations involved and should indicate how the principles in this Declaration have been addressed. The protocol should include information regarding funding, sponsors, institutional affiliations, potential conflicts of interest, incentives for subjects and information regarding provisions for treating and/or compensating subjects who are harmed as a consequence of participation in the research study.

    In clinical trials, the protocol must also describe appropriate arrangements for post-trial provisions.

Research Ethics Committees

23. The research protocol must be submitted for consideration, comment, guidance and approval to the concerned research ethics committee before the study begins. This committee must be transparent in its functioning, must be independent of the researcher, the sponsor and any other undue influence and must be duly qualified. It must take into consideration the laws and regulations of the country or countries in which the research is to be performed as well as applicable international norms and standards but these must not be allowed to reduce or eliminate any of the protections for research subjects set forth in this Declaration.

    The committee must have the right to monitor ongoing studies. The researcher must provide monitoring information to the committee, especially information about any serious adverse events. No amendment to the protocol may be made without consideration and approval by the committee. After the end of the study, the researchers must submit a final report to the committee containing a summary of the study's findings and conclusions.

Privacy and Confidentiality

24. Every precaution must be taken to protect the privacy of research subjects and the confidentiality of their personal information.

Informed Consent

25. Participation by individuals capable of giving informed consent as subjects in medical research must be voluntary. Although it may be appropriate to consult family members or community leaders, no individual capable of giving informed consent may be enrolled in a research study unless he or she freely agrees.

26. In medical research involving human subjects capable of giving informed consent, each potential subject must be adequately informed of the aims, methods, sources of funding, any possible conflicts of interest, institutional affiliations of the researcher, the anticipated benefits and potential risks of the study and the discomfort it may entail, post-study provisions and any other relevant aspects of the study. The potential subject must be informed of the right to refuse to participate in the study or to withdraw consent to participate at any time without reprisal. Special attention should be given to the specific information needs of individual potential subjects as well as to the methods used to deliver the information.

    After ensuring that the potential subject has understood the information, the physician or another appropriately qualified individual must then seek the potential subject's freely-given informed consent, preferably in writing. If the consent cannot be expressed in writing, the non-written consent must be formally documented and witnessed.

    All medical research subjects should be given the option of being informed about the general outcome and results of the study.

27. When seeking informed consent for participation in a research study the physician must be particularly cautious if the potential subject is in a dependent relationship with the physician or may consent under duress. In such situations the informed consent must be sought by an appropriately qualified individual who is completely independent of this relationship.

28. For a potential research subject who is incapable of giving informed consent, the physician must seek informed consent from the legally authorised representative. These individuals must not be included in a research study that has no likelihood of benefit for them unless it is intended to promote the health of the group represented by the potential subject, the research cannot instead be performed with persons capable of providing informed consent, and the research entails only minimal risk and minimal burden.

29. When a potential research subject who is deemed incapable of giving informed consent is able to give assent to decisions about participation in research, the physician must seek that assent in addition to the consent of the legally authorised representative. The potential subject's dissent should be respected.

30. Research involving subjects who are physically or mentally incapable of giving consent, for example, unconscious patients, may be done only if the physical or mental condition that prevents giving informed consent is a necessary characteristic of the research group. In such circumstances the physician must seek informed consent from the legally authorised representative. If no such representative is available and if the research cannot be delayed, the study may proceed without informed consent provided that the specific reasons for involving subjects with a condition that renders them unable to give informed consent have been stated in the research protocol and the study has been approved by a research ethics committee. Consent to remain in the research must be obtained as soon as possible from the subject or a legally authorised representative.

31. The physician must fully inform the patient which aspects of their care are related to the research. The refusal of a patient to participate in a study or the patient's decision to withdraw from the study must never adversely affect the patient-physician relationship.

32. For medical research using identifiable human material or data, such as research on material or data contained in biobanks or similar repositories, physicians must seek informed consent for its collection, storage and/or reuse. There may be exceptional situations where consent would be impossible or impracticable to obtain for such research. In such situations the research may be done only after consideration and approval of a research ethics committee.

Use of Placebo

33. The benefits, risks, burdens and effectiveness of a new intervention must be tested against those of the best proven intervention(s), except in the following circumstances:

    Where no proven intervention exists, the use of placebo, or no intervention, is acceptable; or

    Where for compelling and scientifically sound methodological reasons the use of any intervention less effective than the best proven one, the use of placebo, or no intervention is necessary to determine the efficacy or safety of an intervention

    and the patients who receive any intervention less effective than the best proven one, placebo, or no intervention will not be subject to additional risks of serious or irreversible harm as a result of not receiving the best proven intervention.

    Extreme care must be taken to avoid abuse of this option.

Post-Trial Provisions

34. In advance of a clinical trial, sponsors, researchers and host country governments should make provisions for post-trial access for all participants who still need an intervention identified as beneficial in the trial. This information must also be disclosed to participants during the informed consent process.

Research Registration and Publication and Dissemination of Results

35. Every research study involving human subjects must be registered in a publicly accessible database before recruitment of the first subject.

36. Researchers, authors, sponsors, editors and publishers all have ethical obligations with regard to the publication and dissemination of the results of research. Researchers have a duty to make publicly available the results of their research on human subjects and are accountable for the completeness and accuracy of their reports. All parties should adhere to accepted guidelines for ethical reporting. Negative and inconclusive as well as positive results must be published or otherwise made publicly available. Sources of funding, institutional affiliations and conflicts of interest must be declared in the publication. Reports of research not in accordance with the principles of this Declaration should not be accepted for publication.

Unproven Interventions in Clinical Practice

37. In the treatment of an individual patient, where proven interventions do not exist or other known interventions have been ineffective, the physician, after seeking expert advice, with informed consent from the patient or a legally authorised representative, may use an unproven intervention if in the physician's judgement it offers hope of saving life, re-establishing health or alleviating suffering. This intervention should subsequently be made the object of research, designed to evaluate its safety and efficacy. In all cases, new information must be recorded and, where appropriate, made publicly available.